Validation of the concept of allostatic load in a working context

Thesis

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Contents

1 Introduction

A long time has passed, since Hans Selye introduced the concept of "stress" to the scientific community and to a broad public. Selye used the emergency reaction of the sympathetic nervous system and adrenocortical system to elaborate his classic theory of stress (Selye, 1936). Selye postulated the "General Adaptation Syndrome", a stereotyped physiological response that takes the form of a series of three stages in the reaction to a stressor: (1) In the *alarm reaction* a process of adaptation is promoted and homeostasis is restored by the release of epinephrine from the adrenal medulla and glucocorticoids be the adrenal cortex. (2) In the stage of *resistance*, defence and adaptation are sustained and optimal after homeostasis has been restored. (3) If the stress response persists, adaptive responding ceases and the stage of *exhaustion* follows, which might finally lead to illness and death.

Lazarus and colleagues made an important addition to the understanding of "stress", when they stated their transactional cognitive stress model, emphasizing that stressors are not independent from the individual. Rather, stressors are defined as real *or* interpreted threats to the physical or psychological integrity of an individual (Folkman & Lazarus, 1988; Lazarus & Folkman, 1984). Thereby, the individual's appraisal of a situation received a more central role.

The enormous advances in biomedical research in the past five decades have added more detailed knowledge of the so-called "stress" hormones and their action throughout the body (McEwen, unpublished). These advances had certain implications for the understanding of the stress reaction and therefore for Selye's General Adaptation Syndrome. For example, it is no longer interpreted to mean that there is a stereotyped response of stress mediators to all types of stress. Rather, there are different patterns of response of the different hormone systems that are related to the type of stressor (Chrousos, 1998; Goldstein, 1995). Furthermore, in the light of newer knowledge that the stress mediators can have both protective and damaging effects depending on the time course of their secretion, Selye's "stage of exhaustion" needed also to be reinterpreted.

Giving credit to the classic concepts of Selye and Lazarus, as well as regarding newer evidence, led McEwen in the 1990s to develop a new biological framework in which he conceptualised and measured the cumulative impact of social status, income, education, working and living environments, lifestyle, health related behaviours, and stressful life experiences on physical and mental health (McEwen, 1998; McEwen, 1998b; McEwen & Stellar, 1993). With reference to Sterling and Eyer (Sterling, 1988), McEwen called the final burden that is put on a person's health, "allostatic load". This new concept to assess the effects of psychosocial factors on disease processes has since been validated for elderly people in the MacArthur Studies on Successful Aging (Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997).

But is this model also valid in the context of a younger working population? The present studies were designed to test several hypotheses that the model implies. The focus lies on the role of psychosocial factors within this model. On the one hand their hypothesized influence on physiological parameters is assessed, and on the other hand their proposed effect on health-related behaviour is measured.

In recent years, research on psychosocial factors at work has taken several ways. While some researchers have focused on the amount of job strain that arises from the degree of control and demands the individual experiences (Karasek, 1990), others emphasized the importance of the balance between efforts and rewards (Siegrist, 1996; Siegrist, Peter, Junge, Cremer, & Seidel, 1990). Also, a lot of research has been done identifying pathogenic, health-impairing as well as and salutogenic, health-promoting work conditions without the limitation to a couple of dimensions (Antonovsky, 1979, 1987; Greif, Bamberg, & Semmer, 1991; Kirkcaldy, Cooper, & Ruffalo, 1995; Shigemi, Mino, Tsuda, Babazono, &

Aoyama, 1997; Udris, Kraft, & Mussmann, 1991; Udris, Kraft, Mussmann, & Rimann, 1992; Wilkins & Beaudet, 1998).

Independent from the working context, a new psychosocial notion has been elaborated and shown to bear a predictive validity for manifest health outcomes (Appels, 1990; Appels, Kop, & Schouten, 2000; Appels & Mulder, 1988, 1989; Kop, 1994; Kop, Appels, Mendes de Leon, & Bar, 1996; Kop, Appels, Mendes de Leon, de Swart, & Bar, 1994). This notion refers to a general feeling of fatigue and has been termed “vital exhaustion”. Its association with future cardiac dysfunction has rendered it an importance within the framework of allostatic load.

Apart from psychosocial factors, the area of health psychology has identified a long list of behaviours that influence health (Schwarzer, 1997). Among those with the best-established links to certain health outcomes are cigarette smoking, alcohol consumption, and physical exercise (Boden-Albala & Sacco, 2000; Jensen, Nyboe, Appleyard, & Schnohr, 1991). All above mentioned psychosocial factors and health-related behaviours were taken into account in the present thesis to test the following research questions empirically:

(1) Is there an association between psychosocial factors and physiological parameters related to the concept of allostatic load?
(2) Do psychosocial factors exert an indirect influence on physiological parameters related to the concept of allostatic load via health-related behaviours?

To discuss these research questions, the thesis first presents the central framework of allostatic load from different perspectives in detail including empirical evidence (chapter 2). After an overview on the effects of early experience and development (chapter 3), the relevant psychosocial factors are reviewed (chapter 4). The job strain model of Karasek and Theorell (section 4.3.1) is followed by Siegrist’s effort-reward imbalance model (section 4.3.2), general considerations on the issue of social support at work (section 4.3.3), and an integrative approach centred on the questionnaire SALSA (section 4.3.4). The section on psychosocial factors closes with a summary on the concept of vital exhaustion (section 4.4.1). The last theoretical review deals with the health-related behaviours alcohol consumption (section 5.1), smoking (section 5.2), and physical exercise (section 5.3). Chapter 6 denotes a methodological excourse. Structural equation modelling, a statistical technique that is relevant for one of the researched hypotheses, is presented in summary. In chapter 7 the research objectives are deduced from the theoretical explanations. Chapter 8 presents cross-sectional data from a prospective cohort study on the issue of the association between psychosocial factors and physiological parameters related to the concept of allostatic load. The following chapter 9 addresses the question whether psychosocial factors exert an indirect influence on physiological parameters related to the concept of allostatic load via health-related behaviours. Finally, chapter 10 discusses the results from the two empirical studies first separately and then in the context of the whole framework of allostatic load and in relation to the existing literature. The thesis closes with limitations that have to be considered and implications for future research.

2 The framework of Allostatic Load

The framework of allostatic load is a very broad concept, comprising numerous issues related to the traditional area of “stress” research. McEwen et al. tried to incorporate the most different kinds of stressors, stress-mediating and –moderating variables, biological agents, cognitive, behavioural, and physiological responses, and health outcomes into one generalised model (McEwen, 1998a). A first impression of this model can best be obtained from the following figure.

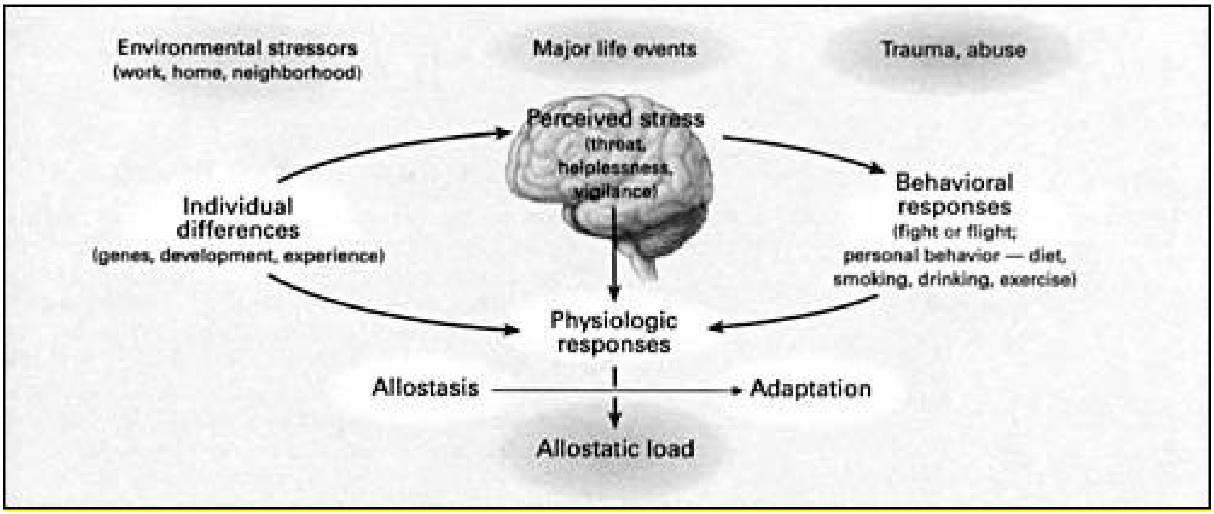

Figure 1. The framework of allostatic load (McEwen, 1998a, p.172).

The complexity of the mechanisms underlying this model, as well as the enormous quantity and variety of empirical evidence that can be subsumed under this model is difficult to be structured. The present thesis answers this challenge by splitting the whole framework into reasonable parts and viewing these parts from different perspectives. By looking at the framework of allostatic load from different angles, the author aims at helping the reader to put the puzzle together and to derive a more holistic view. This approach inevitably leads to some overlap in the different sections on the framework of allostatic load, which is intended.

This chapter focusses on the biological aspects within the above model. It begins with a definition and description of the concepts of allostasis and allostatic load in a narrower sense. It continues with sections on the biological mediators of allostatic load and the systems affected by allostatic load. Then, a classification system is offered that helps to organize the involved biological parameters due to their position in the pathways leading from allostasis to disease. Finally, the empirical validation that has been carried out on the framework of allostatic load is reviewed and methodological aspects for further research in this area are discussed.

2.1 The concepts of Allostasis and Allostatic Load

Allostasis is a term which was first introduced by Sterling and Eyer (Sterling, 1988). They used this term to describe changes in heart rate and blood pressure across time of day as well as changes of these parameters due to experience. Furthermore, they also used this term to describe changes in the set point of these parameters in hypertension. This was actually their primary example to distinguish allostasis from homeostasis. McEwen and Stellar (McEwen & Stellar, 1993) developed this approach further and defined allostasis as the process that actively maintains homeostasis. Homeostasis is a process that keeps a number of systems, which are crucial for survival, within a narrow range. These system are for example pH, body temperature and oxygen tension. While these systems do not play a role in the process of adaptation of the individual to its environment, allostasis is defined as a process that meets perceived or anticipated demands through fluctuating hormones, heart rate and blood pressure, cytokines, and other tissue mediators and hormones (McEwen, unpublished). Therefore, McEwen and colleagues propose, that allostasis is much better a term for physiological coping mechanisms than is homeostasis, which should be reserved for the parameters that are essential for maintaining survival. Allostasis on the other hand should be defined as „maintaining stability through change“ (McEwen, 1998; Price, Lorenzon, & Handa, 2000).

The inefficient management of the allostatic systems is called an „allostatic state“, which in turn leads to „allostatic load“, which denotes the cost of the body for adapting repeatedly to demands placed upon it (McEwen & Stellar, 1993). The most important aspect of the mediators associated with allostasis is that they have protective effects in the short run, but they can have damaging effects over longer periods of time if there are multiple or prolonged demands from the environment, or the secretion of the mediators is dysregulated (McEwen, 1998; McEwen, unpublished). There are four types of response patterns, that describe how the production of the mediators of allostasis give way to a so-called „wear and tear“ on the same systems that they are involved in protecting and promoting adaptation (Figure 2)(McEwen, 1998). The *first* type is simply too much „stress“ in the form of repeated, novel events that cause repeated elevations of stress mediators over long periods of time (McEwen & Seeman, 1999). Lynch et al. showed for example that the amount and frequency of economic hardship predicts decline of physical and mental functioning and increases mortality (Lynch, Kaplan, & Shema, 1997). The *second* type of allostatic load is characterized by a lack of adaptation of the hormonal stress response in response to the repeated occurrence of the same stressor. This leads to an overexposure to the stress mediators. Kirschbaum et al. report an example for this type of response pattern (Kirschbaum et al., 1995). They measured cortisol in a public speaking task, and found a small percentage of individuals, who do not habituate to this task and might possibly overexpose their bodies to stress hormones under many circumstances in daily life that do not affect the majority of other individuals. The *third* type of response pattern regards the failure to either shut off the hormonal stress response or to display the normal trough of the diurnal cortisol pattern. For example, Gerin and Pickering examined individuals with a family history of hypertension and showed prolonged elevation of blood pressure in the aftermath of work-related stress (Gerin & Pickering, 1995). Further examples for the perturbation of the diurnal rhythm are, that sleep deprivation leads to elevated evening cortisol and hyperglycemia (Leproult, Copinschi, Buxton, & Van Cauter, 1997; Plat et al., 1999; Spiegel, Leproult, & Van Cauter, 1999), and depressive illness leads to elevated cortisol and loss of bone mineral (Michelson et al., 1996; Sapolsky, Krey, & McEwen, 1986). Finally, the *fourth* type of response pattern involves an inadequate hormonal stress response that allows other systems, such as inflammatory cytokines, to become overreactive. In an animal model the Lewis rat is an example for increased susceptibility to inflammatory and autoimmune disturbances related to inadequately low levels of cortisol (Sternberg, 1997, 1996). Comparable human disorders in which too low levels may play a role include fibromyalgia and chronic fatigue syndrome (Buske-Kirschbaum et al., 1997; Crofford et al., 1994; Heim, Ehlert, Hanker, & Hellhammer, 1998; Poteliakhoff, 1981; Ur, White, & Grossman, 1992).

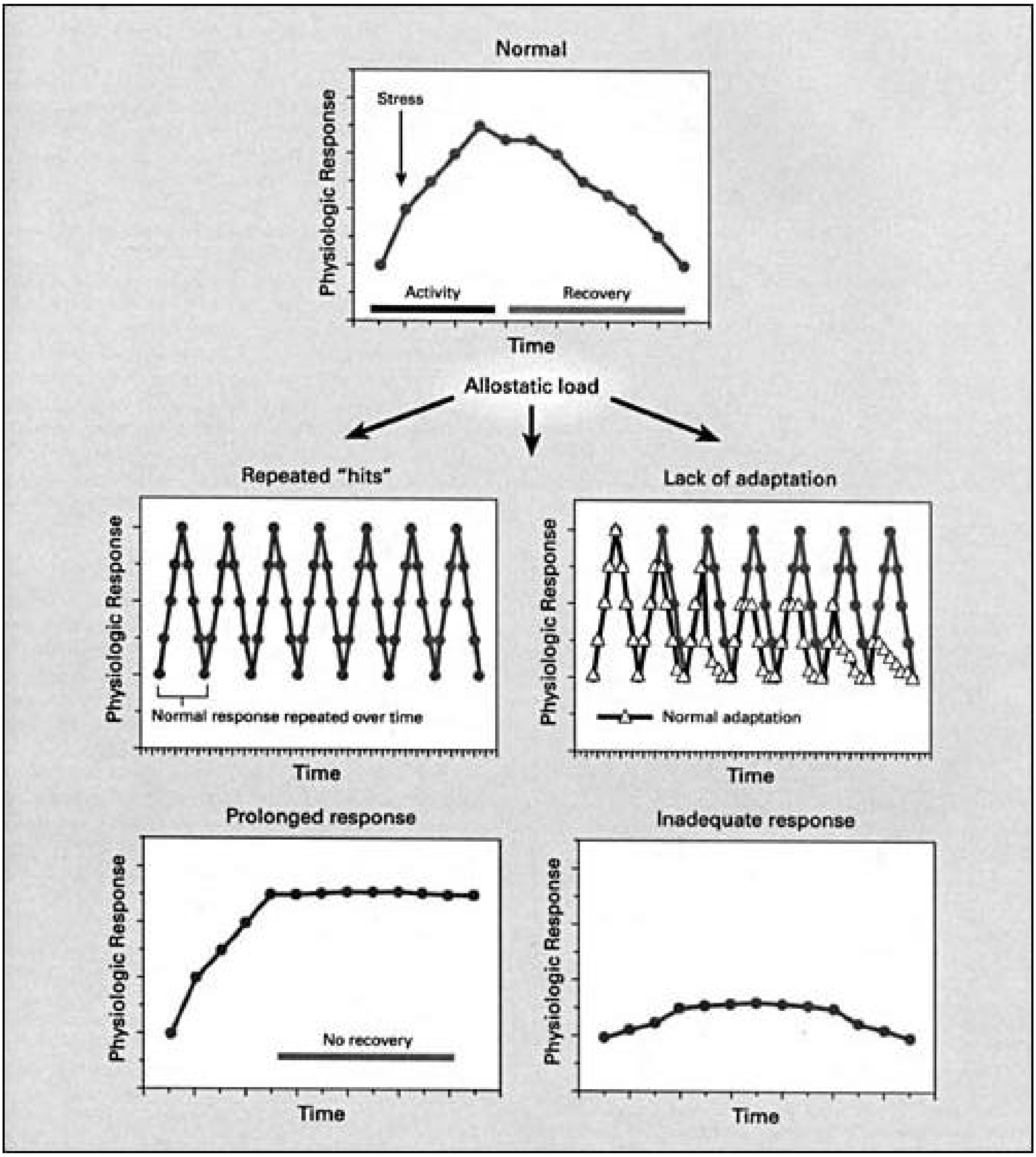

Figure 2. Four types of inadequate stress reactions.

2.2 Biological mediators and dysregulated adaptive systems that contribute to allostatic states and allostatic load

The major goal within the framework of allostatic load is to answer the question, how working environments, living environments and socio-economic conditions affect health or disease. If one follows the events that lead to disease over the life course in individual humans, there are two different endpoints that can possibly be measured. One refers to the response profiles of the mediators themselves and has been introduced as allostatic states. The other one is referred to as allostatic load and focuses on the tissues and organs that show the cumulative effects of overexposure to these mediators.

The choice of mediators that can finally be measured in an actual study depends upon a series of practical considerations. Amongst these are the size of the study, cost of the assays, and not wanting to disrupt the lives of the subjects more than necessary, so as to retain cooperation on the one hand and not to influence the secretion of the measured mediators by additional stress or anxiety on the other hand. Therefore, the applied methods to assess the mediators should be as non-invasively as possible. This surely favours collecting urine and saliva samples, if necessary blood, and only under special circumstances cerebrospinal fluid. Due to their easy applicability saliva samples are most attractive. Also very easy to obtain is information on blood pressure and heart rate through portable monitoring. This is one of the reasons why the study of cardiovascular function as an endpoint of disease has progressed further than that of other systems of the body that are sensitive to stress and show allostatic load (McEwen, unpublished).

In the following paragraphs, the connection and contribution to allostatic load is presented for the most widely acting and easily measured mediators of allostasis: glucocorticoids, DHEA, and catecholamines. These mediators affect many different body systems in various ways, and their production and actions are inter-connected with each other.

2.2.1 Glucocorticoids

Glucocorticoids have multifarious regulatory effects on the human body. Virtually every tissue in the body has intracellular glucocorticoid receptors (Sapolsky, Romero, & Munck, 2000). In regard to the cardiovascular system, glucocorticoids enhance cardiovascular function in times of acute stress. Part of this effect is mediated by enhanced catecholamine sensitivity. As for hemorrhagic stressors, glucocorticoids suppress the increase in fluid volume to avoid harm from an excessive response to damage. The most well known effect of glucocorticoids is to suppress inflammation in the acute phase response to an infection. Thus, they keep they enhance initial mobilization of immune cells to sites of infection and shape the nature of the immune response. In relation to metabolism, glucocorticoids serve the neogenesis of glucose, while promoting lipolysis and proteolysis. On a more behavioural level they promote appetite and food-seeking behaviour. Glucocorticoids generally antagonize the effects of insulin, except under chronic glucocorticoid elevation. Then, they nearly reverse their effects, promote lipogenesis that leads to fat deposition, and impair insulin production in a way that finally can lead to Type II diabetes.

The stimulation of appetite for food by glucocorticoids opposes the rather anorectic effect of CRF, a precursor of cortisol in the hormonal cascade of the HPA axis. In the central nervous system, glucocorticoids inhibit the transport of glucose into brain cells and promote the catecholamines' effect of enhancing cardiovascular activity and thereby cerebral blood flow. Another effect of glucocorticoids on the CNS relates to the memory function. Here, glucocorticoids act in two opposing ways. While basal levels enhance emotionally charged memory formation, stress levels suppress memory. There is even evidence, that repeated stress levels lead to glucocorticoid-mediated atrophy in regions of the brain, that serve the memory function. A final system, in which glucocorticoids are involved, is the reproductional system. Not only is it evolutionary logical not to mate in times of stress, but also do glucocorticoids themselves participate in mechanisms that inhibit reproduction.

In conclusion, glucocorticoids are mediators that are very suitable to measure the concept of allostatic load. They can easily be measured non-invasively by saliva samples and they give information about a wide variety of normal and pathophysiological conditions. Elevated levels of glucocorticoids have been related empirically to many conditions including hypertension, abdominal obesity, bone mineral loss, loss of muscle mass, suppression of immune responses, memory impairment, and atrophy of brain structures. Chronically low levels of glucocorticoids on the other hand are known to contribute to increased inflammatory and autoimmune responses, conditions of imbalance of cytokines, pain mechanisms in fibromyalgia, and chronic fatigue syndrome (McEwen, unpublished).

2.2.2 Dehydroepiandrosterone (DHEA)

DHEA is a functional antagonist of glucocorticoids (Browne, Porter, Correa, Abadie, & Svec, 1993; Kalimi, Shafagoj, Loria, Padgett, & Regelson, 1994; Wolf & Kirschbaum, 1999). "Functional antagonist" means that DHEA does neither interact with the glucocorticoid receptor, nor is there any known receptor for DHEA in any tissue at all. Rather, DHEA counters the effects usually exerted by glucocorticoids. For example, it antagonizes the thymolytic actions of glucocorticoids (Blauer, Poth, Rogers, & Bernton, 1991), as well as the suppression of inflammatory cytokine production and cellular and humoral immune responses (Kalimi et al., 1994). The reciprocal relation of glucocorticoids and DHEA can also be seen in the correlation between bone mineral loss and reduced levels of DHEA in response to glucocorticoid therapy for autoimmune and inflammatory disorders (Formiga et al., 1997; Robinzon & Cutolo, 1999).

In the CNS, evidence seems to mount that DHEA interacts with the neurotransmitter systems of serotonin, GABA, excitatory amino acids and dopamine, although details are not clear

(Abadie et al., 1993). Nonetheless, there are reports of reduced depressive symptomatology in elderly due to DHEA (Wolkowitz et al., 1997), which might either be attributable to its glucocorticoid antagonizing actions or to its interaction with the serotonin system. Recently, DHEA has been propagated as a possible neuroprotective agent in aging (Wolf & Kirschbaum, 1999), which basically stems from enhanced memory effects in aged rats, but could not be shown for cognitive functioning in human subjects so far.

Regarding all empirical evidence, DHEA seems to be a potentially useful measure for the amelioration of the pathophysiological effects exerted by the glucocorticoids. Especially the level of DHEA in relation to glucocorticoids promises a valid assessment of allostatic load.

2.2.3 Catecholamines

Catecholamines are another important class of mediators of allostasis. Their effects sometimes synergise with the effects of glucocorticoids and at other times oppose them. The various effects of catecholamines are discussed with regard to the different body systems they affect.

Concerning cardiovascular function, the sympathetic nervous system depletes catecholamines to maintain cerebral blood flow in the transition from lying to standing, as well as during upright physical activity. Disorders of the sympathetic nervous system occur for example in congestive heart failure, where activity is increased in the face of declining sensitivity of the heart to respond to the catecholamines (Goldstein, 2000).

As for inflammation and immunity, catecholamines are involved in the mobilization and redistribution of immune cells in the body (Spencer, 2000), while decreasing both T-cell and

NK cell functions but not the proliferation of splenic B cells (Dowdell, 2000). The metabolic system is affected by the catecholamines in the same way as by the glucocorticoids regarding glucose and lipids, and in the opposite way regarding proteins. There is some evidence mounting, that elevated levels of norepinephrine and glucocorticoids in combination with decreased levels of adrenal medullary epinephrine contribute to insulin resistance, hyperglycemia, and in the end to Type II diabetes (Arauz-Pacheco et al., 1996; Bjorntorp, Holm, & Rosmond, 1999). The roles the catecholamines play in the CNS comprise attention, vigilance, and arousal functions (Goldstein, 2000), as well as the formation of memories that are associated with strong emotions.

To sum it up, the catecholamines are related to changes in emotional state, physical activity, metabolism and body temperature, and cardiac function. Epinephrine and norepinephrine are somewhat independent and represent adrenal medullary and sympathetic neural activity, respectively. Therefore, it seems indicated to measure both hormones or their metabolites in blood and urine. Elevated levels of these hormones, especially at night, when acvtivity is usually decreased, are indicative of an allostatic state that may add to allostatic load, if occurring chronically.

2.3 Systems affected by allostatic load

From the above sections on mediators of allostatic load you can see, that various systems of the body are affected. The following sections report some findings for three of the most important body sytems: the cardiovascular system, the brain, and the immune system.

2.3.1 The cardiovascular system

The best-studied system of allostasis and allostatic load is the cardiovascular system and its links to obesity and hypertension (McEwen, 1998a). In animal studies with primates, the incidence of atherosclerosis was increased among the dominant males of unstable social hierarchies and in socially subordinate females (Manuck, Kaplan, Adams, & Clarkson, 1988; Shively & Clarkson, 1994). For humans, Bosma et al. (Bosma et al., 1997) showed, that lack of control on the job increases the risk of coronary heart disease. There are also results showing that job strain leads to elevated blood pressure and an increased left-ventricular-mass index (Schnall, Schwartz, Landsbergis, Warren, & Pickering, 1992), as well as increased progression of atherosclerosis (Everson et al., 1997). Chronic stress like feelings of fatigue, lack of energy, irritability, and demoralization, as well as hostility are linked to increased reactivity of the fibrinogen system and of platelets, both of which increase the risk of myocardial infarction (Markowe et al., 1985; Raikkonen, Lassila, Keltikangas-Jarvinen, & Hautanen, 1996). This connection has also been shown for the conecpt of vital exhaustion (Appels, 1990; Appels, Falger, & Schouten, 1993).

2.3.2 The brain

Repeated stress does also have an impact on brain functioning. This holds true especially for the hippocampus, which has high concentrations of cortisol receptors (McEwen, De Kloet, &

Rostene, 1986). The hippocampus is involved in that part of the verbal memory that is accountable for the spatial and temporal context of highly emotional events (Eichenbaum, Otto, & Cohen, 1992; LeDoux, 1995). This process itself is mediated by glucocorticoids (Pugh, Tremblay, Fleshner, & Rudy, 1997). If the hippocampus is impaired, then contextual memory lacks reliability and accuracy. This phenomenon again may exacerbate stress, because one cannot accurately appraise a situation in terms of its potential threat (Sapolsky, 1990). Moreover, the hippocampus has also an inhibiting function on the HPA axis‘ response to stress (Herman & Cullinan, 1997; Jacobson & Sapolsky, 1991). In that sense, the impairment of the hippocampus is a self-reinforcing process.

Acute stress increases cortisol secretion, which impairs short-term memory in the hippocampus and temporal lobe (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; McEwen & Sapolsky, 1995). Fortunately, this effect is reversible and only of a short duration (Lupien & McEwen, 1997). Repeated or chronic stress over months and years on the other hand causes atrophy of dendrites in the hippocampus and may even kill hippocampal neurons in the long run (McEwen et al., 1995; Sapolsky, 1992; Uno, Tarara, Else, Suleman, & Sapolsky, 1989). For stress-related disorders like recurrent depressive illness, post-traumatic stress disorder, and Cushing’s disease, an association with hippocampal atrophy could be shown (McEwen & Magarinos, 1997; Sapolsky, 1996). To date, it remains elusive, whether this atrophy is reversible or permanent. In rats, long-term stress contributes to age-related neuronal damage (Choi, 1988; Kerr, Campbell, Applegate, Brodish, & Landfield, 1991; Kerr, Campbell, Thibault, & Landfield, 1992; Lowy, Wittenberg, & Yamamoto, 1995; Mattson, 1992; Mills & Kater, 1990) and potentiates atrophy and possibly even neuronal loss.

2.3.3 The immune system

The immune system responds to pathogens or other antigens with its own form of allostasis that may include an acute-phase response as well as the formation of an immunologic „memory“ (McEwen, 1998a). The HPA and the autonomous nervous system on the other hand tend to dampen cellular immunity (McEwen et al., 1997). However, not all effects are suppressive. Acute stress enhances the traffic of lymphocytes and macrophages to the site of the acute challenge (Dhabhar, 1996; Dhabhar & McEwen, 1996). This immuno-enhancing effect is in part mediated by glucocorticoids (Dhabhar, Miller, McEwen, & Spencer, 1995; Dhabhar, Miller, Stein, McEwen, & Spencer, 1994; Herbert & Cohen, 1993; McEwen et al., 1997; Miller et al., 1994), and lasts for three to five days. The result of acute stress is presumably beneficial, if the immunologic memory is of a pathogen or tumor cell. Yet, if the immunologic memory leads to an autoimmune or allergic response, then stress is likely to exacerbate a pathologic state. The outcome is completely different in the event of repeated stress, which increases allostatic load. Certain types of the immune response (i. e. delayed hypersensitivity) are substantially inhibited rather than enhanced (Dhabhar, McEwen, 1996). One consequence of this suppressed cellular immunity is for example an increased severity of the common cold (Cohen, Tyrrell, & Smith, 1991).

2.4 From allostasis to disease

When regarding the various physiological systems and their mediators, allostatic load reveals a problem. Within the original conceptualisation of allostatic load, its components were not organized and categorized with regard to what each measure represents in the cascade leading from allostasis to allostatic load (McEwen & Seeman, 1999). Also, the original measures were not systematically chosen in a way that would facilitate relating them to specific diseases, or adding new measures as a consequence of new research evidence on pathways and mechanisms leading from these measures to disease. Therefore there was a need for a concept that relates what is measured to a pathophysiological process. To satisfy this need, McEwen and Seeman formulated the notion of primary mediators leading to primary effects and then to secondary outcomes, which finally lead to tertiary outcomes that represent actual diseases (McEwen & Seeman, 1999). The following sections outline this concept in detail.

2.4.1 Primary Mediators

At present, the concept of allostatic load comprises four primary mediators: cortisol, norepinephrine, epinephrine, and DHEA. These primary mediators have widespread influences on the body and are very powerful in predicting a variety of secondary and tertiary outcomes, when measured correctly.

As noted above, cortisol is a glucocorticoid with various influences throughout the body. Cortisol receptors are found in virtually every tissue and organ in the body. Cortisol is released in response to stressful events in a cascade known as the HPA axis. The hypothalamus releases the corticotropin-releasing factor (CRF), which then stimulates the pituitary to release adrenocorticotropin-releasing hormone (ACTH) in the adrenal. The adrenal finally releases cortisol, which effects various target tissues and organs, including a negative feedback to the brain, which stops further release of CRF (Chrousos et al., 1995; Fisher & Reason, 1988; McEwen, 2000; Steptoe, 2000)(see figure 3).

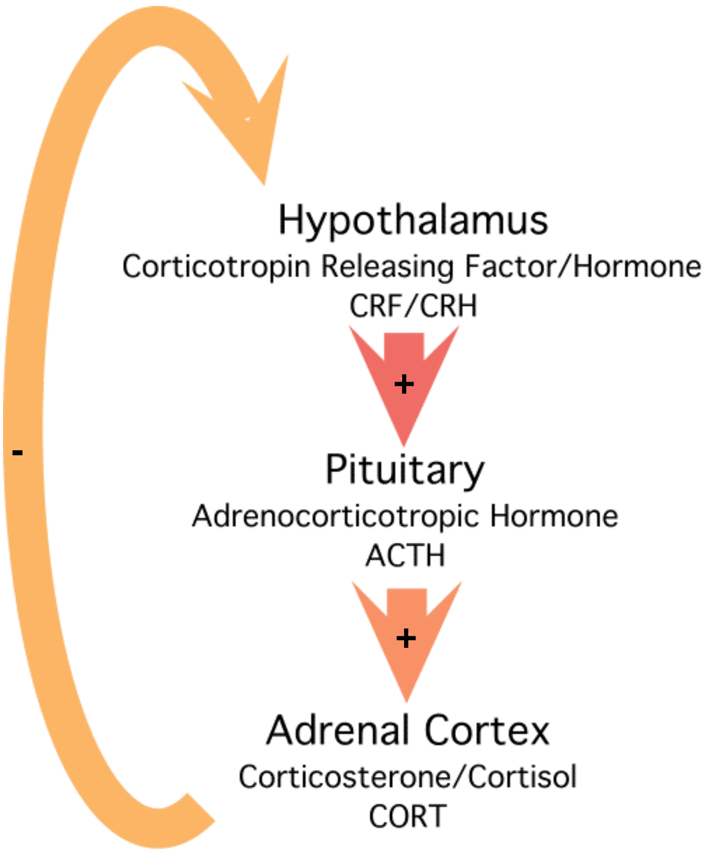

Figure 3. The HPA-axis.

Cortisol mediates different effects ranging from induction of liver enzymes involved in energy metabolism to regulating the trafficking of immune cells and cytokine production (McEwen, 1993) to facilitating formation of fear-related memories (Quirarte, Roozendaal, & McGaugh, 1997). The functional antagonist of cortisol is DHEA (May, Holmes, Rogers, & Poth, 1990; Wright, Porter, Browne, & Svec, 1992), although there are also effects of DHEA that are independent from antagonizing cortisol, like preserving immocompetence after thermal injury (Araneo & Daynes, 1995). Generally, low levels of DHEA are considered deleterious

(Morales, Nolan, Nelson, & Yen, 1994), as is chronically high cortisol. It is important to keep in mind that the acute release of stress mediators is generally adaptive and aims at achieving stability through change, i. e. maintaining homeostasis. As noted earlier, this process is labelled allostasis. Allostatic load on the other hand arises from the chronic elevation or dysregulation of these mediators over long times and finally causes problems.

Epinephrine and norepinephrine are catecholamines that are released by the adrenal medulla and the sympathetic nervous system. Like glucocorticoid receptors, adrenergic receptors are also widespread throughout the body, in blood vessels and target organs such as the liver, pancreas, and the brain. The effects of these catecholamines range from vasoconstriction and acceleration of heart rate to trafficking of immune cells to targets, as well as enhancement of fear-related memory formation (Cahill, Prins, Weber, & McGaugh, 1994). It is also the chronic dysregulation of these mediators that leads to a cascade of events, which is further outlined below.

2.4.2 Primary Effects

Primary effects represent the link between the dysregulation of the primary mediators and the secondary outcomes. Yet, primary effects are not measured within the concept of allostatic load, although this might be a much desirable task for future research. The notion of primary effects tries to elucidate the mechanism, by which primary mediators exert their influences.

Glucocorticoids for example regulate gene expression via several pathways, involving interactions with DNA via the glucocorticoid response elements and also via protein-protein interactions with other transcriptional regulators (Miner, Diamond, & Yamamoto, 1991). As noted above, the role of DHEA is a glucocorticoid-antagonizing one.

The catecholamines act via alpha and beta adrenergic receptors. Beta adrenergic receptors then stimulate the formation of the intracellular second messenger cAMP, which, in turn, regulates intracellular events via phosphorylation (Siegel, 1999). Animal models have shown, that in some cases, glucocorticoid and cAMP pathways converge at the level of gene expression (Yamada, Duong, Scott, Wang, & Granner, 1999). Therefore it is not surprising that the secondary outcomes described below are the result of more than one primary mediator.

2.4.3 Secondary Outcomes

The secondary outcomes, included in the original allostatic load concept, are all related to abnormal metabolism and risk for cardiovascular disease and include the following parameters: waist-to-hip-ratio, blood pressure, glycosylated hemoglobin, cholesterol/HDL ratio, and LDL. Amongst these parameters, waist-to-hip-ratio and glycosylated hemoglobin reflect the effects of sustained elevations in glucose and the insulin resistance that develops as a result of elevated cortisol and elevated sympathetic nervous system activity (McEwen & Seeman, 1999). Blood pressure elevation is a primary indication that can lead to accelerated atherosclerosis as well as insulin resistance. In addition, it is part of the pathophysiological pathway of the metabolic syndrome. Cholesterol, HDL and LDL serve as measures of metabolic imbalance related to obesity and atherosclerosis and are also influenced by the same primary mediators as well as by other metabolic hormones.

There is long list of additional secondary outcomes that are worth being regarded within the concept of allostatic load. Possible expansions of the assessment of allostatic load are discussed further below in the “Methodological Aspects”-section.

2.4.4 Tertiary Outcomes

According to McEwen and Seeman, tertiary outcomes are “actual diseases or disorders that are the result of the allostatic load that is predicted from the extreme values of the secondary outcomes and of the primary mediators.” (McEwen & Seeman, 1999) p. 40). Thus far, only very few tertiary outcomes have been investigated. Most of the empirical evidence on the allostatic load concept stems from the MacArthur studies of successful aging. In these studies only cardiovascular disease, decreased physical capacity, and severe cognitive decline have been investigated with regard to their relation with allostatic load (Seeman, McEwen, Singer, Albert, & Rowe, 1997; Seeman, Singer et al., 1997). Following the new concept of the cascade of primary mediators, primary effects, secondary outcomes, and tertiary outcomes, decline in physical capacity and cognitive functioning would have to be regarded as secondary outcomes, rather than tertiary outcomes. That leaves cardiovascular disease as the only actual disease investigated to date in relation with allostatic load. Apart from additional primary mediators and secondary outcomes to be included in the measurement of allostatic load, there is going to be a need to include additional tertiary outcomes like cancer.

The benefits of this new conceptualisation include the possibility to relate the progression of pathophysiology from primary mediators via secondary outcomes to actual disease. Furthermore, clusters of secondary outcomes can be identified that relate to particular diseases. Thus, this concept supplies a theoretical framework that extends beyond the correlational search for potential risk factors for disease.

2.5 Validation of the concept of Allostatic Load

The concept of allostatic load was first empirically tested within the MacArthur studies of successful aging (Seeman, McEwen et al., 1997; Seeman, Singer et al., 1997). Seeman et al. assessed parameters from the HPA and sympathetic nervous systems, as well as from the cardiovascular system and metabolic processes (Seeman, Singer et al., 1997). They concentrated themselves on higher, chronic, steady-state levels of activity or failure to shut off responses to acute stressors in their assessment of allostatic load. Thus, they only assessed single measures of physiologic activity rather than the dynamics of these systems in response to challenge.

In the MacArthur study of successful aging the following parameters were measured (Seeman, Singer et al., 1997):

- Systolic and diastolic blood pressure, indices of cardiovascular activity.
- Waist-to-hip-ratio, an index of more chronic levels of metabolism and adipose tissue deposition.
- Serum HDL and total cholesterol, related to the development of atherosclerosis.
- Blood plasma levels of glycosylated hemoglobin, an integrated measure of glucose metabolism over several days' time.
- DHEA-S, a functional HPA axis antagonist.
- Overnight urinary cortisol excretion, an integrated measure of 12-hour HPA axis activity.
- Overnight urinary epinephrine and norepinephrine excretion levels, integrated indices of 12-hour SNS activity.

For each of the above 10 indicators, subjects were classified into quartiles. Allostatic load then was generated by summing up the number of parameters for which the subject fell into the highest risk quartile. This was the lowest quartile for HDL and DHEA-S, and the top quartile for all other parameters.

This measure of allostatic load was then examined for its ability to predict health outcomes over a 2.5-year follow-up. Higher allostatic load scores were found to predict significantly increased risks for incident cardiovascular disease as well as increased risks for decline in physical and cognitive functioning and for mortality (Seeman, Singer et al., 1997). With the data from this longitudinal cohort study, first empirical evidence for the validity of the concept of allostatic load has been gathered on a prospective basis.

2.6 Methodological aspects

The assessment of allostatic load faces an inherent discrepancy between the theoretically optimal assessment and the practically possible. It would be optimal to assess a kind of basic or usual level of allostatic mediators, as well as the range the system parameters in response to stimulation. Furthermore, an allostatic load score should contain parameters for all major physiological regulatory systems. These demands are countered with the practicability of an empirical study.

The MacArthur studies of successful aging showed, that the originally chosen markers bore a meaningful relationship with pathophysiological outcomes. There are a number of suggestions for additional parameters to assess allostatic load. In the MacArthur studies, the secondary outcomes used were those that related to the metabolic syndrome and cardiovascular disease. It might be helpful to also include the measurement of circulating cytokines such as IL-1, IL-6 and TNF-alpha for their relation to another set of disorders related to inflammatory and autoimmune disorders or to the opposite, such as substantially suppressed immune function as a result of chronic stress. Further disorders which are linked to a dysregulation of cytokine production are chronic fatigue syndrome and fibromyalgia (Dhabhar, Satoskar, Bluethmann, David, & McEwen, 2000; Moldofsky, 1995). The cytokine markers will probably not show strong links with metabolic and cardiovascular disorders (McEwen, unpublished). This multi-factoriality has to be borne in mind when interpreting associations with an allostatic load summary score.

Additional markers that also have been proposed to be included in the measurement of allostatic load comprise body mass index (Hecker, Kris-Etherton, Zhao, Coval, & St Jeor, 1999; Lakka, Lakka, Salonen, Kaplan, & Salonen, 2001), high sensitivity C-reactive protein and tumor-negrosis factor alpha as markers of inflammatory activity (Appels, 1999; Koenig et al., 1999; Lindahl, Toss, Siegbahn, Venge, & Wallentin, 2000; Mendall et al., 2000; Ridker, Hennekens, Buring, & Rifai, 2000), and microalbuminuria and sodium excretion as markers of sub-clinical renal dysfunction (Gerstein et al., 2001; Jensen, Feldt-Rasmussen, Strandgaard, Schroll, & Borch-Johnsen, 2000).

In the MacArthur studies of successful aging, allostatic load was calculated by summing the number of parameters for which the subject fell into the “highest” risk quartile. Seeman et al. (Seeman, Singer et al., 1997) also tried alternative ways of calculating allostatic load, including setting the criterion for high risk stricter at the top (or bottom) 10% of the distribution of each parameter. They also used averaged z-scores as a measure of allostatic load. Although they report essentially the same results for all alternatives, using the highest risk quartiles yielded the strongest effects. This goes along with the idea that relatively higher values on various parameters are indicative for allostatic load, rather than only the most extreme values. On the other hand, simply averaging levels of activity across systems might obscure effects that only affect several, but not all, systems.

Although Seeman and McEwen (McEwen & Seeman, 1999) reported that they weighted the 10 original components of allostatic load equally based on factor analysis, which yielded equally high loadings on factors representing different physiologic systems, they lateron noted, that “different biological systems should be weighted differently according to the health outcomes to be predicted” (Seeman et al., 2001). This has subsequently been done based on canonical correlation analyses, but not yet been published (Karlamangla, unpublished).

A further methodological problem concerns the measurement of the primary mediators (glucocorticoids, catecholamines, DHEA, and cytokines). Apart from the problem to assess these dynamic systems over the course of time, their plasma levels may also be related to such factors as recent exercise, allergies, sleep deprivation, and persistence of viral and other infections that exacerbate the existing allostatic state (Borish et al., 1998; Cannon et al., 1999; Kavelaars, Kuis, Knook, Sinnema, & Heijnen, 2000; Mawle et al., 1997; Moldofsky, 1995; Peterson et al., 1994). This issue allows reliable assessment of the primary mediators only under highly standardized study conditions.

3 Early life experience and development

In his allostatic load model, McEwen hypothesizes on influence both on the perception of stress and the subsequent physiologic response by “individual differences” (see figure 1, p. 10). Under this term he subsumes genes, development, and experience. The following paragraphs discuss the meaning of early life experiences and development for the concept of allostatic load. The aspect of genes does not find consideration, because it would be beyond the scope of this thesis.

Early life experiences as a child are one of the most important factors affecting life-long health. Cold or unstable parent-child relationships or even outright abuse can lead to behavioural and physical problems throughout adult life (McEwen & Seeman, 1999). Individuals who were abused as children show increased mortality and morbidity, which concerns various diseases (Felitti et al., 1998). A recent review showed, that families that are characterized by lack of warmth and support, or parental overregulation or underregulation of children’s behaviour, are also associated with increased physical and mental health risks for children (Repetti, 1999). For these so-called “risky families” also an altered physiological regulation could be shown. Such families exhibit dysregulated HPA activity, primarily higher levels of activity. Further evidence also points to a dysregulation of the serotonergic function (Kaufman et al., 1998; Pine, 1998). These dysregulations might lead to various behavioural dispositions and manifest diseases that are also shown to be related to child abuse and early neglect. Evidence in this area of research includes associations with substance abuse, hostility, aggression, suicide, hippocampal atrophy and cognitive impairment, as well as increased incidence of heart disease, cancer, chronic lung disease, extreme obesity, and liver disease (Felitti et al., 1998; Wadhwa, Sandman, Chicz-DeMet, & Porto, 1997). Low birthweight, which may be caused by stress of the mother, has also been shown to be a risk factor for Type II diabetes, and thus a pathway for the life-long influence of early events (Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993).

Many of these studies in humans are restricted to correlational approaches, but there is evidence mounting from nonhuman primate and rodent models, which seems to support the hypothesized causal relationship. These animal studies provide an attractive model for understanding some environmental and developmental influences on individual differences in human stress reactivity as well as its consequences. For example neonatal “handling” of newborn rats has been shown to produce lower HPA reactivity and slower rates of brain aging measured in terms of cognitive function, whereas prenatal or postnatal stress led to higher HPA activity and increased rates of brain aging (Dellu, Mayo, Vallee, Le Moal, & Simon, 1994; Liu et al., 1997; Meaney, Aitken, van Berkel, Bhatnagar, & Sapolsky, 1988). There is similar evidence in humans which relates elevated levels of cortisol to individual differences in brain aging (Liu et al., 1997; Lupien et al., 1998; Seeman, McEwen et al., 1997), although connections with early life events are sparse. Only recently, early deprivation has been shown to result in elevated reactivity of the HPA and in its consequence to decreased length growth in children (“psychosocial dwarfism”), early-onset major depression and various deviations in cognitive and emotional functioning (Gunnar, 1992; Gunnar, Bruce, & Grotevant, 2000; Gunnar, Bruce, & Hickman, 2001; Gunnar, Morison, Chisholm, & Schuder, 2001).

In conclusion, the health effects of trauma and other childhood adversities appear not to be specific for one type of psychiatric or other disorder, but rather very broad (Felitti et al., 1998; Kessler, Davis, & Kendler, 1997). In a sense, the breadth and strength of the reported effects show some similarity with the broad systemic effects of alterations of the responsiveness of physiological mediators that is embodied in the concept of allostatic load (McEwen & Seeman, 1999). Despite its importance within the concept of allostatic load, aspects of early life experience and development were not assessed in the empirical studies included in this thesis, because the research focus was rather on the influence of psychosocial factors at work.

4 Psychosocial Factors

The following chapter deals with the role of psychosocial factors within the framework of allostatic load. In McEwen's model (figure 1, p.10), psychosocial factors are primarily interpreted as "environmental stressors", although some psychosocial factors may also be interpreted as "individual differences". What is a psychosocial factor? In their systematic review on psychosocial factors in the aetiology and prognosis of coronary heart disease, Hemingway and Marmot define a psychosocial factor as "a measurement that potentially relates psychological phenomena to the social environment and to pathophysiological changes" ((Hemingway & Marmot, 1999), p. 1).

This is a very versatile definition to work with. It renders the possibility to close the gap between the social environment and its health consequences in the individual. The link is established by psychosocial factors that can be measured in the individual. Psychometric techniques have contributed to improve the validity and reliability of questionnaire-based instruments that are used to quantify the relevant psychosocial factors. The use of psychosocial factors bears one great advantage: it avoids the unhelpful general term "stress". Rather than using this term that can be defined in so many different ways (McEwen, 2000; Selye, 1977; Semmer, 1997), this thesis employs psychosocial factors to generate specific hypotheses within the framework of allostatic load that can be tested.

What might be the mechanisms that link psychosocial factors to disease? It is important to answer this question to enable causal inferences from correlational associations to allow deductions for the design of preventive interventions. Also, it should be borne in mind that psychosocial factors may act alone or combine in clusters (Williams et al., 1997), and that they may exert their effects at different stages of the life course (Kuh, 1997). Currently, three different pathways that are interrelated are discussed (Hemingway & Marmot, 1999). (I) Psychosocial factors may affect health related behaviours such as smoking, diet, alcohol consumption, or physical activity, which in turn may influence the risk of certain diseases or disorders (Pieper, LaCroix, & Karasek, 1989). This pathway is incorporated in McEwen's allostatic load model (see figure 1, p.10). McEwen hypothesizes a link from perceived stress (expressed as a psychosocial factor that can be measured in the individual) via behavioural responses (including health related behaviours) to physiologic responses that represent allostatic load (McEwen, 1998a). If health behaviour does actually lie on the causal pathway between psychosocial factors and health outcomes, then the numerous studies that treat health behaviour as a confounding variable must be questioned. (II) Psychosocial factors may also exert a direct causal influence on acute or chronic physiological changes. This pathway is also represented in McEwen's allostatic load model and underlines the interrelation or at least co-existence of various pathways. (III) Finally, psychosocial factors, e. g. social support, might influence access to and content of medical care, although there is little direct evidence for this (Hemingway & Marmot, 1999). This pathway is not explicitly represented in McEwen's model, but it can theoretically be subsumed under the existing notion of mediating "behavioural responses".

If one traces the chain of causation further back, one might want to consider the determinants of psychosocial factors. Here, associations have been reported for socio-economic status (Kaplan & Keil, 1993; Marmot, Bosma, Hemingway, Brunner, & Stansfeld, 1997; Mittleman, Maclure, Nachnani, Sherwood, & Muller, 1997). Within the theory of allostatic load McEwen proposes the roots for psychosocial factors in a number of circumstances, comprising environmental stressors from work, home and neighbourhood, major life events, trauma and abuse, genetic predispositions, development and experience (especially early experience)(McEwen, 1998a).

The following sections of this chapter deal with several psychosocial factors that have been shown to bear relevance for health. The reviewed literature is in each case restricted to health outcomes related to cardiovascular disease. This has been done for two reasons.

Firstly, cardiovascular disease is the field in which most research work has been done. The reasons for that again are that cardiovascular disease remains the major cause of death in the civilized world (Lopez & Murray, 1998; Morrow, Hyder, Murray, & Lopez, 1998; Murray, 1996) on the one hand, and that measurement and monitoring of major risk factors for cardiovascular disease can easily be done (McEwen, 1998b). Secondly, the original allostatic load score contains ten components, of which six can be attributed to cardiovascular disease. So, for the evaluation of the validity of the allostatic load concept, its correctness with regard to cardiovascular disease is a central issue.

When reviewing the epidemiological literature on cardiovascular disease, the psychosocial factors that have been most rigorously tested are: type A/hostility, depression and anxiety, work characteristics, and social support (Hemingway & Marmot, 1999). The research evidence on type A/hostility and depression and anxiety is only summarized briefly, whereas work characteristics and social support are reviewed in more detail. This distinction is made with reference to the focus of this thesis, which is on the validity of the allostatic load concept in a working context and not on personality traits or emotional states.

4.1 Type A/hostility

Type A is characterized by hard driving and competitive behaviour, a potential for hostility, pronounced impatience, and vigorous speech stylistics. The National Institutes of Health declared Type A an independent risk factor for coronary heart disease on the basis of early positive findings in the Framingham Study (Haynes, Feinleib, & Kannel, 1980) and the Western Collaborative Group's eight year follow up (Rosenman, Brand, Sholtz, & Friedman, 1976). Later on there were some negative findings (Hearn, Murray, & Luepker, 1989; Johnston, Cook, & Shaper, 1987; Shekelle et al., 1985), and it was proposed that only the hostility component of type A behaviour might have an aetiological relevance. Five prognostic studies that tried to link type A or hostility to coronary heart disease failed to show an increased risk (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989; Case, Heller, Case, & Moss, 1985; Jenkinson, Madeley, Mitchell, & Turner, 1993; Ragland & Brand, 1988; Shekelle et al., 1985).

4.2 Depression and anxiety

The relation between depression and anxiety and coronary heart disease differs from that of other psychosocial factors. Depression and anxiety themselves represent well defined psychiatric disorders. Furthermore, depression and anxiety are often a consequence of coronary heart disease, which makes it difficult to investigate the actual temporal sequence of these conditions. Finally, depression and coronary heart disease could share common antecedents like environmental stressors or social support.

Despite all these considerations, there is strong evidence for an association between depression and anxiety on the one hand and coronary heart disease on the other hand. Eleven prospective aetiological studies that were chosen for their high methodological quality, all yielded positive results for the proposed association (Anda et al., 1993; Appels & Mulder, 1988; Aromaa et al., 1994; Barefoot & Schroll, 1996; Everson et al., 1996; Hagman, Wilhelmsen, Wedel, & Pennert, 1987; Haines, Imeson, & Meade, 1987; Hallstrom, Lapidus, Bengtsson, & Edstrom, 1986; Kawachi et al., 1994; Kubzansky et al., 1997; Wassertheil-Smoller et al., 1996). This result is also supported by 6 prognostic studies (Ahern et al., 1990; Barefoot et al., 1996; Denollet et al., 1996; Frasure-Smith, Lesperance, & Talajic, 1995; Kop et al., 1994; Ladwig, Roll, Breithardt, Budde, & Borggrefe, 1994).

4.3 Work characteristics

When reviewing the literature on the association between work characteristics and disease in general or cardiovascular disease in particular, one certainly comes across two theories about health related work characteristics. One is the job strain model by Karasek and Theorell (Karasek, 1990) and the other one is the effort-reward imbalance model by Siegrist (Siegrist, 1996, 2000; Siegrist, Klein, & Voigt, 1997).

4.3.1 Job strain model

Karasek and Theorell describe the psychosocial work environment in their job strain model with the use of two dimensions. The control dimension, also called job decision latitude, can be defined as the workers ability to use skills or the decision-making authority available to the worker (Karasek, 1990). This dimension comprises the individual's possibility to explore new methods and ways of doing the job, learn new skills, take responsibility, be independent, develop and use his or her skills and knowledge, and experience variation at work (Lundberg, 2000). The second dimension of the job strain model refers to the psychological demands the worker faces at his workplace. High and low levels on these two dimensions "psychological demands" and "decision latitude" interact to generate four distinctly different kinds of psychosocial work experience: high-strain jobs, active jobs, low strain jobs, and passive jobs (the two-dimensional model is shown in figure 4).

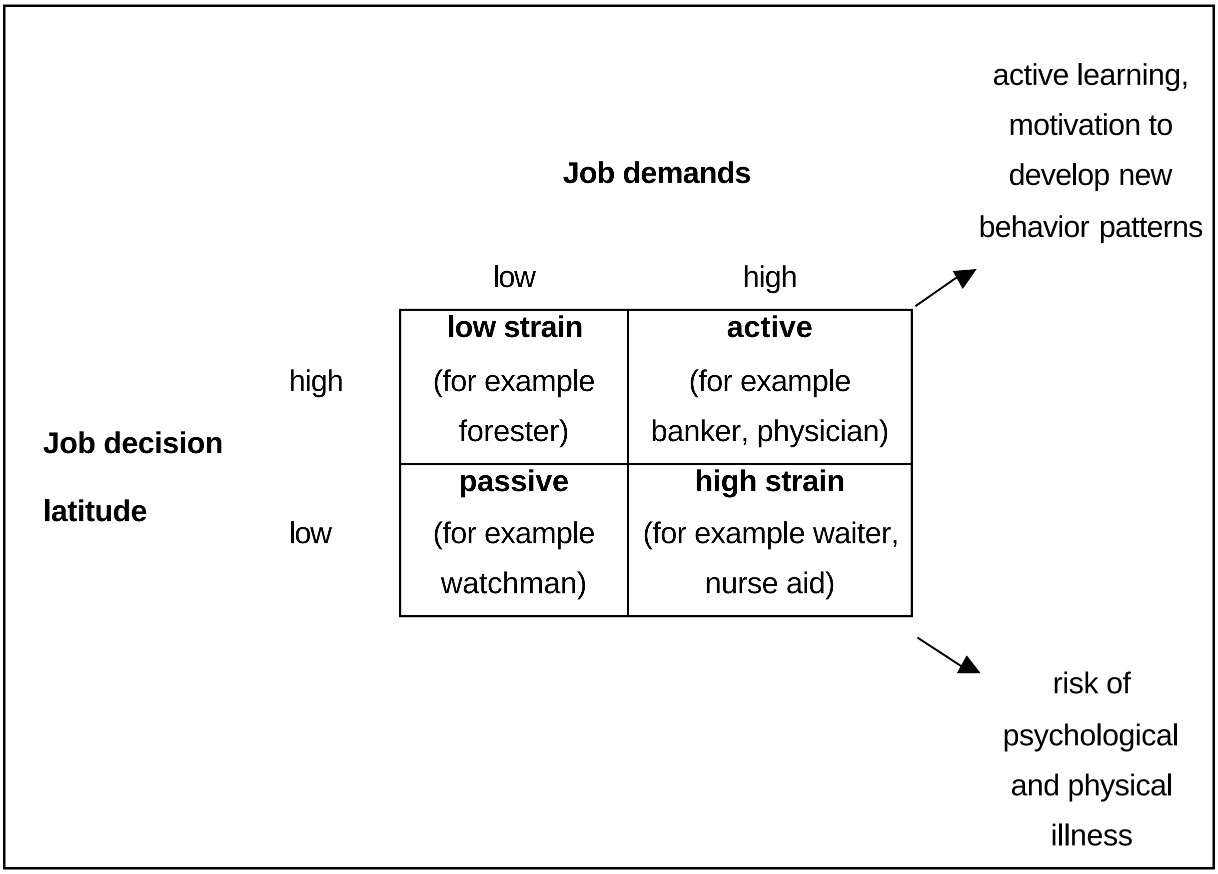

Figure 4. The job-strain model ((Karasek, 1990), p. 32).

Karasek and Theorell predict that the most adverse reactions of psychological strain, including fatigue, anxiety, depression, and physical illness, occur when the psychological demands of the job are high and the worker's decision latitude in the task is low (Karasek, 1990). Such jobs are called high-strain jobs, like for example being a waiter or being a nurse. Most empirical evidence referring to the job strain model could confirm that high job strain is associated with adverse health outcomes, in particular cardiovascular events, compared to low strain jobs like being a forester or being a researcher (Bosma et al., 1997; Kawakami et al., 2000; Lacroix, 1984; Lynch, Krause, Kaplan, Salonen, & Salonen, 1997; Netterstrom, Nielsen, Kristensen, Bach, & Moller, 1999; Riese, Van Doornen, Houtman, & De Geus, 2000; Sacker, Bartley, Frith, Fitzpatrick, & Marmot, 2001; Schnall, Landsbergis, & Baker, 1994;

Steenland, Johnson, & Nowlin, 1997; Steptoe, Cropley, & Joekes, 1999; Su, 2001; Tsutsumi, Kayaba, Tsutsumi, & Igarashi, 2001; Yoshimasu et al., 2000).

Jobs characterized by low demands but also by low decision latitude are called passive jobs. An example for a passive job is being a watchman. Such a job is associated with very nonenergetic responses, but also lacking the desirable aspects of relaxation of the low strain jobs. This situation can be described as a kind of helplessness (Seligman, 1975), but has yet not been related to adverse health outcomes. The same goes for the so-called active jobs, which are characterized by high levels of psychological demands, but also high levels of decision latitude. This combination is often found in high-status jobs like bankers and physicians. Surprisingly, this active work situation has not been associated with increased health risks so far. This inconsistency offers a starting point for criticism. The demand dimension might suffer from the missing distinction between psychological and physical demands, as well as from the missing distinction between qualitative and quantitative demands. We will see in the following sections, how this omission can be overcome.

One further deficit of the job strain model has been identified by the authors themselves and has already been ameliorated. Karasek and Theorell included social support at the workplace as a moderating factor in their model (Karasek, 1990), to take the beneficial effects of workplace social support or the harmful effects of missing social support into account. Recently, a situation characterized by high strain work and social isolation, termed “iso-strain work”, has been shown to go along with adverse health outcomes (Amick et al., 1998). The role social support plays for health will be discussed in more detail further below.

4.3.2 Effort-reward imbalance

Another model for the influence of the working environment on the worker's health is the effort-reward imbalance model by Siegrist (Siegrist, 2000). In contrast to the job strain model, the effort-reward imbalance model does not incorporate the social support component explicitly within its assessment of stressful experiences at work. The model contains one intrinsic and two extrinsic components. One of the extrinsic components refers to the demands and obligations put on the working person and parallels the demand component from the Karasek and Theorell job strain model. The other extrinsic component refers to rewards that the working person receives as so-called social exchange in terms of money, esteem, security or career opportunities. The intrinsic component, finally, refers to personal reward expectancies and the ability to cope with demands.

The model claims that stress results from an imbalance of high extrinsic effort and low intrinsic reward, from a high level of overcommitment, or a combination of both (Siegrist, 2000). In other words, a state of emotional distress is thought to arise from the lack of reciprocity between costs and gains, which is hypothesized to lead to the arousal of the autonomic nervous system and associated stress reactions. If this condition becomes chronic, it results in adverse long-term health outcomes (Bakker, Killmer, Siegrist, & Schaufeli, 2000; Peter & Siegrist, 1997; Siegrist, 1996; Siegrist, Klein et al., 1997; Siegrist, Peter, Cremer, & Seidel, 1997).

Large prospective cohort studies showed associations for high effort and low reward with angina and doctor diagnosed ischemia (Bosma, Peter, Siegrist, & Marmot, 1998), incident of fatal or non-fatal coronary heart disease (Siegrist et al., 1990), hypertension, LDL, HDL, and total cholesterol (Peter et al., 1998), and subjective health functioning and newly reported psychiatric disorders (Stansfeld, Bosma, Hemingway, & Marmot, 1998).

As noted earlier, the effort component of the effort-reward imbalance model resembles the demand component of the job strain model. The difference between the two models therefore reduces to the choice of the second dimension. The word “choice” is used in this context to highlight the arbitrariness incorporated in these models. While one model employs a control dimension, referring to specific task characteristics, the other model employs a reward dimension, emphasizing the importance of social exchange independently from the actual task characteristics. The inherent difficulty of deciding to use one of the models has led to some studies that tried to combine the both of them (Bosma et al., 1998; de Jonge, Bosma, Peter, & Siegrist, 2000; Marmot, Siegrist, Theorell, & Feeney, 1999).

4.3.3 Social support

The hypothesis that health can be affected by supportive interactions with individuals within one’s social network has now been confirmed by a wealth of evidence that emphasizes the the role the social environment plays in health status generally (Berkman, 1983; Broadhead et al., 1983; Wallston, 1983) and in cardiovascular disease risk specifically (for an overview see (Shumaker, 1994)). Stressful life events in the personal, social, occupational, or marital realm may have important consequences, and social support may aid in the reduction of emotional distress and problems within these realms. Furthermore, social support is proposed to play a crucial role in coping with physical disability, illness or injury (Davidson, 1979; Porrit, 1979; Wallston, 1983). Therefore, it is widely accepted in the medical, public health, and psychological literatures that social support enhances health outcomes (Cohen & Syme, 1985). None the less, systematic investigation of this issue is faced with a variety of caveats and considerations (Kaplan, 1994).

One distinction that has to be considered is that between the structure of a person's social environment and the resources of functions such environments provide. The structure is usually referred to as one's "social network" and includes the size, density, complexity, symmetry, and stability of an individual's family, friends, co-workers, health professionals and community resources (Shumaker, 1994). The functional component of social support, often simply labelled "social support", is defined as an individual's perception of the availability of support and of the resources provided. As you can see, the term social support does not always apply to the same theoretical construct and often describes both structural and functional aspects (Shumaker, 1984).

A variety of measures have been used to assess social support from both a structural and functional perspective. But there are further aspects that have to be regarded. Support-disease models vary in terms of the effect they propose. While some state a direct influence of support on pathogenic process in terms of a main effect, others hypothesize a stress-buffering effect that decreases the risks created by psychosocial stressors (Cohen & Wills, 1985). The stability of the support characteristic under consideration is also an important issue. Especially with regard to cardiovascular disease, conceptions of social support that are stable over longer periods of time make more sense than conceptions that vary considerably, because atherosclerosis is a disease that also develops over long periods of time. Blazer (Blazer, 1982) showed that all these considerations are crucial, when he found that the magnitude of the relationship between social support and risk of 30-month mortality depended on the definition of social support. Finally, when thinking about which measure is most appropriate for a particular project, it requires considering which aspects of social support fit most logically with the particular indices of health and well-being at interest.

A recent review of prospective aetiological and prognostic cohort studies showed that odds ratios for the influence of social support on cardiovascular disease vary widely (Hemingway & Marmot, 1999). Nevertheless, five of eight prospective cohort studies found positive effects of social support on fatal coronary heart disease and all cause mortality rates (Berkman, Breslow, 1983; House, Robbins, & Metzner, 1982; Medalie & Goldbourt, 1976; Orth-Gomer, Rosengren, & Wilhelmsen, 1993; Vogt, Mullooly, Ernst, Pope, & Hollis, 1992). The same goes for nine of ten prognostic studies (Berkman, Leo-Summers, & Horwitz, 1992; Case, Moss, Case, McDermott, & Eberly, 1992; Chandra, Szklo, Goldberg, & Tonascia, 1983; Friedmann & Thomas, 1995; Gorkin et al., 1993; Hedblad et al., 1992; Ruberman, Weinblatt, Goldberg, & Chaudhary, 1984; Wiklund et al., 1988), the relative risks for three of these studies exceeding 3.

4.3.4 An integrative approach to work characteristics and social support at work

In contrast to the classical quest for stressful conditions in the environment leading to pathogenesis, the researchers around Rimann and Udris were looking for conditions and resources that serve the maintenance and restoration of health (Rimann, 1993; Udris et al., 1992; Udris, 1994). This approach follows the concept of salutogenesis by Antonovsky (Antonovsky, 1979, 1987). On the basis of systemic and action-based models health is defined positively, i. e. not only as the absence of disease. Very similar to the definition of allostasis, health is thought of as a dynamic balance within the individual as well as between the individual and its environment. The permanent maintenance or restoration of this balance, respectively, depends on the use of internal (personal) and external (situational, organisational, and social) health resources. Personal resources comprise cognitive belief systems (Hurrelmann, 1991), locus of control (Krampen, 1991; Liu et al., 2000; Rader, Krampen, & Sultan, 1990; Rotter, 1966), hardiness (Kobasa, 1982), optimism (Scheier et al., 1999), self-efficacy (Bandura, Cioffi, Taylor, & Brouillard, 1988; Schwarzer & Renner, 2000), and sense of coherence (Antonovsky, 1993) amongst others. Organisational resources comprise task characteristics that facilitate the individual's ability to cope and deal with demands of their work or to tolerate or avoid them, like task variety, time buffers, opportunities to learn, communicate, cooperate or participate. Finally, social resources include cooperative superior behaviour, social support by superiors and co-workers, and a positive working climate.

Following all these considerations, Rimann and Udris (Rimann, 1993) came up with a questionnaire called “Salutogenetische Subjektive Arbeitsanalyse (SALSA)”. SALSA is a combination of existing instruments for work analysis (Caplan, 1982; Greif et al., 1991; Hackman, 1975; Karasek, 1990; Richter, 1984) and newly formulated questions and items by the authors. As outlined earlier in this paragraph, the focus lies on salutogenesis on the one hand and on the assessment of subjective appraisals on the other hand. The latter is based on the assumption that most working conditions are neither pathogenic nor salutogenic in themselves. It is rather the combination of stressors and resources that develops its impact in the course of the actions that lead to the performance of the work task.

The validity and reliability of the SALSA has been proven in data from 1655 workers in the secondary and tertiary sectors (Länger, 1995; Rimann, 1993). The results showed that the appraisal of strains and resources at work depend to a large degree on task characteristics and working conditions. Effects of sex and age were negligible. Several subscales of the SALSA have also been shown to be able to predict burnout and its components as measured by the Maslach Burnout Inventory (German translation by Enzmann (Enzmann, 1989)) in ursing staff (Nerdinger, 1999).

Taking into account all reviewed models and evidence on work-related stress and health, four conclusions can be drawn so far: (1) an important dimension of work stress refers to the strain, which is exerted on the individual by external and internal, physical and psychological demands or efforts. (2) The concept of social support, in whatever kind it may be defined or operationalized, plays a crucial role for health. (3) Not only do pathogenic factors play a role concerning health, but also should salutogenic factors be taken into consideration. (4) The central role the individual perception of stressful events and conditions plays within the framework of allostatic load in particular (McEwen, 1998a), as well as in leading transactional stress theories in general (Lazarus & Folkman, 1984), seems to indicate the use of methods to assess subjective ratings of the concerned events and conditions over attempts to objectify them.

4.4 “Perceived stress”

A central role in the theoretical framework of allostatic load is played by the notion of “perceived stress” (see figure 1, p.10). McEwen paraphrases “perceived stress” in his model with threat, helplessness, and vigilance (McEwen, 1998a). In this thesis, more emphasis is put on the term “perceived”, in the sense of subjective well-being or feelings of being “stressed”, exhausted or ill. On the one hand it is well-known that subjective feelings of well-being, emotions like anger and anxiety or depressive mood may contribute to psychiatric disorders like post traumatic stress disorder (Baumann & Perrez, 1998; Ehlert & Hellhammer, 2000; Steptoe, Cropley, Griffith, & Kirschbaum, 2000). On the other hand, many studies showed that subjective ratings of stress or discomfort do not necessarily correlate with either physiological mediators of stress like cortisol (Kirschbaum & Hellhammer, 1999) or physiological reactions that are typically related to stressful events like heart rate and skin conductance level (Steptoe & Noll, 1997). It is therefore important not only to measure “objective” physiological changes and ratings of psychosocial factors like task characteristics and social support, but also to assess the health status of the individual as he/she perceives or defines it himself/herself. For the above reasons, three constructs to assess perceived well-being or health status were employed in the present studies, which will be described in the following paragraphs.

4.4.1 Vital exhaustion

Excess fatigue and feelings of general malaise are among the most prevalent precursors of myocardial infarction and sudden cardiac death (Kop, 1994). Estimates of the percentage of people who experienced “undue fatigue” or “lack of energy” before a cardiac event ranged from 13% to 70% (Alonzo, Simon, & Feinleib, 1975; Feinleib, Simon, Gillum, & Margolis, 1975; Gillum, Feinleib, Margolis, Fabsitz, & Brasch, 1976; Klaeboe, Otterstad, Winsnes, &

Espeland, 1987; Kuller, 1972; Rissanen, Romo, & Siltanen, 1978; Simon, Feinleib, & Thompson, 1972; Stowers & Short, 1970; Thiele, 1985; Wolf, 1969). The reason for this wide range lay in the most different questions asked to coronary patients in order to examine this issue. Discontent with this situation led Appels and colleagues to form the initial conceptualisation of vital exhaustion in the late 1970s. They followed the classical procedure of test construction to come up with the initial scale, which was subsequently tested in two case-control studies (Appels, 1980; Verhagen, Nass, Appels, van Bastelaer, & Winnubst, 1980). The final construct of vital exhaustion had three defining characteristics: (1) feelings of excess fatigue and lack of energy; (2) increased irritability; and (3) feelings of demoralization (Appels & Otten, 1992). Subsequently, a series of prospective and case-control studies were performed that showed that age-adjusted risk of angina pectoris and that of non-fatal myocardial infarction was significantly increased in individuals with higher values of vital exhaustion (Appels & Mulder, 1989). In a study on myocardial infarction in women, the relative risk associated with exhaustion, after controlling for age, smoking, coffee consumption, diabetes, hypertension, non-anginal pain, and menopausal status was 2.75 (Appels et al., 1993). Furthermore, vital exhaustion predicted new cardiac events after successful coronary angioplasty (Kop, 1994), and the association between exhaustion and future myocardial infarction was shown not be confounded with underlying coronary disease (Kop et al., 1996).

There are also studies, showing that vital exhaustion bears relevance for the working context. Falger showed that working overtime was related with both vital exhaustion and myocardial infarction and that overwork appears to be a risk factor for manifest coronary disease especially if it results in a state of exhaustion (Falger & Schouten, 1992). “Exhaustion after work”, which assessed the impact of work on daily life rather than merely time spent working, has been shown to be the best single expression of the influence of quantitative job demands on coronary morbidity (Sihm, Dehlholm, Hansen, Gerdes, & Faergeman, 1991).

Vital exhaustion is a construct that shows some overlap with the concepts of depression, burnout, and chronic fatigue syndrome, but the similarities and differences cannot be discussed in detail within this thesis. The interested reader is asked to refer to Gaab for chronic fatigue syndrome (Gaab, 2001), Maslach and colleagues for burnout (Maslach, Jackson, & Leiter, 1996; Maslach & Leiter, 2000), and Raikkonen for depression in relation to vital exhaustion (Raikkonen et al., 1996). Especially for depression, there are studies claiming that vital exhaustion and depressive symptomatology are differently associated with behavioural risk factors for coronary artery disease (Kopp, Falger, Appels, & Szedmak, 1998), as well as studies denying that depression and vital exhaustion bear significantly different conceptual identities (Wojciechowski, Strik, Falger, Lousberg, & Honig, 2000).

The roles of the health behaviours smoking, alcohol consumption, and physical exercise are discussed in the following section. The influence of sleep is excluded from the list of health behaviours, because it cannot willingly be influenced like the others. Nevertheless, there is evidence that although exhausted persons do not spend less time sleeping, the restorative properties of their sleep are less efficient (van Diest, 1990) and that being exhausted on waking up is predictive of future myocardial infarction (Appels & Schouten, 1991).

In addition to the concept of vital exhaustion with its well-founded empirical evidence in relation to cardiovascular disease, two other instruments were used in the present studies to gain measures on subjective well-being and health status. One was the German version of the short form of the General Health Questionnaire (Bullinger & Kirchberger, 1998). This questionnaire contains a physical and a mental health summary score that are well validated and have been shown to be measures that are able to reflect changes in subjective well-being due to several diseases and disorders (Arnold, Witzeman, Swank, McElroy, & Keck, 2000; Failde & Ramos, 2000; Hollingworth et al., 2002; Mosconi, Cifani, Crispino, Fossati, & Apolone, 2000; Ware, 2000).

The second instrument is a symptom checklist, which was used in a nationwide health survey in Germany (Burke, 1999). This checklist is applied for reasons of comparability with a standardized sample of the German population as well as for assessing the degree of somatisation, which is a concept that might be confounded with the measurement of health outcomes (Ng & Norwood, 2000).

5 Behavioural responses – health-related behaviour

The final component of the allostatic load model that has not yet been discussed is that of the behavioural responses. The examples McEwen gives as behavioural responses comprise fight or flight, diet, smoking, drinking, and exercise (McEwen, 1998a). Since fight or flight has only an indirect influence on an individual's health status, the focus in this thesis is on the other behaviours, which are more directly linked to health outcomes.

The influence of the diet is very specific, e. g. depending on which fatty acids exactly are contained in the consumed food (Grundy & Denke, 1990; Nestel, 1991; Riemersma et al., 1986; WHO, 1990; Wood, 1992). This makes the accurate assessment of the relevant aspects of the diet almost impossible. Therefore, only smoking, alcohol consumption, and physical exercise were measured in the present studies, for which the literature will be reviewed briefly in the following paragraphs.

5.1 Alcohol consumption

There is consistent and almost unanimous agreement that the curve for the relationship between alcohol consumption and total mortality rates is U-shaped (Marmot & Brunner, 1991). Alcohol has an adverse effect on hypertension, which increases the risk for stroke. Also, high intakes of alcohol are associated with cardiomyopathy and a high incidence of cardiac arrhythmias. On the other hand, the risk for coronary heart disease is greater for non-drinkers. This effect has been attributed to several confounding factors (WHO, 1994). The group of non-drinkers might for example include people who gave up drinking because they were unwell. Lifelong non-drinkers have also been labelled as an unusual group in a society in which some alcohol is the norm. Nevertheless, these factors do not provide enough evidence that the increased coronary risk for non-drinkers is not real (Marmot & Brunner, 1991; Rimm et al., 1991; Shaper, 1990). Neither do the effects of the confounding factors cigarette smoking, social class, diet and inaccuracies in taking down or giving information on drinking habits explain this phenomenon. It can therefore be concluded, that moderate drinking (10-30g of ethanol daily) provides a moderate protective effect against cardiovascular disease, as compared with abstention and heavy drinking (Criqui, 1990).

From Mediterranean countries we know, that mortality from coronary heart disease is low despite a high intake of saturated fat. This effect has been attributed to the high wine consumption in these countries (Renaud & de Lorgeril, 1992). To date it remains unclear, whether this effect is mediated by non-alcoholic constituents of wine. A recent review on this issue has been done by Wollin and Jones (Wollin, 2001). However, the U-shaped curve has been demonstrated sufficiently often in populations where wine does not account for the major part of alcohol consumed (WHO, 1994).

5.2 Smoking

American and British national health institutions have done extensive reviews on several large cohort studies examining the effects of smoking (Marmot, Shipley, & Rose, 1984; Marmot, 1978). These reviews concluded that cigarette smoking was causally related to disease and that smoking cessation substantially reduced the risk of cancer, respiratory disease, coronary heart disease, and stroke. There was a dose-response curve between the number of cigarettes smoked and the relative risk of stroke, while the evidence was a little less strong for coronary heart disease (Goldblatt, 1990; Haan, Kaplan, & Camacho, 1987).

The evidence on the rather political issue of passive smoking suggests that passive smoking is associated with a small increase in the risk of coronary heart disease (He et al., 1999). Given the high prevalence of cigarette smoking, the public health consequences of passive smoking with regard to coronary heart disease may be more important than the actual risk for the individual.

After all, cigarette smoking remains the most important preventable cause of premature death for example in the United States, accounting for about 430700 of the more than 2 million annual deaths (American Heart Association Homepage, 2000).

5.3 Physical activity

In the 1950s epidemiological studies were published that began to link physical activity to decreased incidence of myocardial infarction and sudden death. Physically active workers have been found to have fewer heart attacks than more sedentary fellow-workers (Morris, 1953; Paffenbarger, 1982; Taylor, 1962). Additionally, in more recent studies exercise outside work has been examined and it has been shown that physical inactivity, whether occupational or recreational, is associated with increased risk of coronary heart disease independently of other risk factors (Berlin & Colditz, 1990; Caspersen, 1989; Leon, Connett, Jacobs, & Rauramaa, 1987; Paffenbarger, Hyde, Wing, & Hsieh, 1986; Powell, Thompson, Caspersen, & Kendrick, 1987). Exercise apparently protects against coronary heart disease by mechanisms affecting blood pressure, obesity, serum lipoprotein profiles, and insulin resistance (WHO, 1994).

Since 1992, 17 large, well-conducted prospective, non-randomised studies have specifically examined the association between physical activity and risk of non-fatal and fatal coronary heart disease (Dorn et al., 1999; Eaton et al., 1995; Folsom et al., 1997; Fraser, Strahan, Sabate, Beeson, & Kissinger, 1992; Gartside, Wang, & Glueck, 1998; Haapanen, Miilunpalo, Vuori, Oja, & Pasanen, 1997; Hakim et al., 1999; Jensen et al., 1991; Leon, Myers, & Connett, 1997; Lindsted, Tonstad, & Kuzma, 1991; Luoto, Prattala, Uutela, & Puska, 1998;

Rodriguez et al., 1994; Rosolova, Simon, & Sefrna, 1994; Sherman, D'Agostino, Cobb, & Kannel, 1994; Simonsick et al., 1993; Stender, Hense, Doring, & Keil, 1993; Woo, Ho, Yuen, Yu, & Lau, 1998). These studies showed that people who are physically active typically experience 30-50% reductions in relative risk of coronary heart disease compared with people who are sedentary, after adjustment for other risk factors. The absolute risk for sudden death after strenuous activity is small and does not outweigh observed benefits . All available evidence on the issue of the effects of physical activity led Russell and colleagues to the recommendation that every adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week (Russell, 1995).

6 The Structural Equation Modeling Approach

The following chapter represents a methodological excourse. For one of the research objectives, it is helpful to understand the basics of the method of structural equation modelling. Structural equation modeling (SEM) is a comprehensive statistical approach to testing hypotheses about relations among observed and latent variables (Hoyle, 1995). This excourse is a summary for persons, who are familiar with basic statistics like regression analysis and ANOVA. Nevertheless, it is *not* crucial for the general comprehension of the empirical studies to understand SEM in detail.

6.1 Model Specification

SEM begins with the specification of a model to be estimated. But what do the terms model and specification mean? A model is a statistical statement about the relations among variables. A correlation, for example, specifies a nondirectional relation between two variables. In multiple regression analysis and ANOVA directional relations between a single or multiple independent variables and a single dependent variable are specified. Although, of course, directionality cannot be tested statistically by those approaches.

Specification is the exercise of formally stating a model. For a simple correlation, the only model that can be specified is a single nondirectional relation between two variables. In ANOVA usually main effects and interactions are considered, which need no further model specification. Explicit specifications on behalf of the investigator comprise planned comparisions. Exploratory factor analysis for example begins without any explicit model. In SEM on the other hand specification is crucial. No analysis can take place until the researcher has explicitly specified the relations among the variables to be analyzed. In SEM a whole set of parameters needs specification. These parameters are constants which indicate the nature of the relation between the variables in the model. Although there is no limitation as to specify the magnitude or sign of these parameters, usually they are only specified as either being free or being fixed. Fixed parameters are not estimated from the data and are usually fixed at zero. The free parameters are those, that the researcher believes to be nonzero and which are estimated from the data.

The degree to which the pattern of fixed and free parameters is consistent with the variances and covariances in the data indexes model adequacy. The various possibilities to assess model adequacy (i. e. goodness-of-fit) will be discussed later in this section.

The pattern of fixed and free parameters also defines two parts of the general structural equation model: the *measurement model* and the *structural model*. In the measurement model the latent variables are prescribed. Latent variables are unobserved variables, which are implied by the covariances between two or more indicators or observed variables. They are often also called factors and are free of measurement error as well as free of uniqueness associated with their indicators. Confirmatory factor analysis is a method that uses only the measurement model. The structural model on the other hand describes the relations among latent variables and those observed variables, that do not serve as indicators. In this sense, multiple regression analysis can be compared to the structural model, but limited to a single outcome variable and not taking measurement error into account. The combination of measurement model and structural model makes up for a statistical approach, which is capable of evaluating relations among variables without measurement error.

The relations between variables, whether they are latent or observed, can be of three different kinds. First, there is the nondirectional association. This association corresponds to a usual correlation. Second, there is the direct effect, which is exerted from an independent variable on a dependent variable. This kind of relation can also be found in classical ANOVA and multiple regression analyses. The third kind of effect is the indirect effect. It is characterized by a variable exerting an influence on another variable via one or more intervening or mediating variables, which act as dependent and independent variables at the same time. The sum of direct and indirect effects of one variable onto another is often referred to as total effect.

6.2 Identification

The concept of identification is crucial to the structural equation modelling approach. It needs substantial consideration within the process of model specification. Identification refers to the relation of the parameters to be estimated in the model – i. e. the free parameters – and the information that is available from the data – i. e. the observed variances and covariances. The whole issue of identification circles around one question. Can for every free parameter in the model a single, unique value be obtained from the data? If the answer to this question is ‚yes', then you call the model *just identified* and it has zero degrees of freedom. If there are multiple ways to obtain values for the free parameters, then the model is *overidentified* with the degrees of freedom equal to the number of observed variances and covariances minus the number of free parameters. This is the kind of condition, which you need to evaluate the adequacy of a model. In contrast to the *just identified* model, where the model always fits perfect to the data, the *overidentified* model contains so-called restrictions, which make it more difficult to find a set of parameters which represents the observed variances and covariances best within the pre-specified model. If there are more free parameters in the model than observed variances and covariances, you call the model *underidentified.* In this case, the parameters cannot be estimated.

The determination of the identification status of a model can be quite tricky. There are rules of thumb that should be obeyed when specifying a model (Davis, 1993; Grayson, 1994; Rigdon, 1995), but there is no guaranty that this leads to an identified model. Computer programms usually give warnings, when encountering underidentification, but often they do not state the location of the identification problem.

6.3 Estimation

Once a model has been specified, the next step is to estimate the free parameters from the observed variances and covariances. For this task iterative methods such as maximum likelihood or generalized least squares are used. Iterative means in this context, that start values are chosen for the free parameters. This can be done by the researcher, but it is usually left to computer programms. Then the matrix of variances and covariances is calculated, which is implied by these tentative values and the fixed parameters. This implied covariance matrix is then compared with the actual covariance matrix from the data. The difference between the two is called residual matrix. Each further step in the iterative process changes the values for the free parameters with the aim of minimizing the residuals matrix, i. e. bringing the implied covariance matrix as close to the actual covariance matrix as possible. The iteration continues until the covariances which are implied by the estimated parameters cannot get any closer in magnitude and direction to the actual covariances. At this point in time the estimation procedure is said to have converged.

When the estimation procedure has converged to a solution, a single number is produced, which characterises how close the implied covariance matrix is to the actual covariance matrix. This number is called value of the fitting function and approaches zero as the implied covariance matrix gets closer to the actual matrix. An actual value of the fitting function of zero means that there is a perfect match between the two matrices. The value of the fitting function is the basis for all evaluations of the so-called goodness-of-fit.

6.4 Evaluation of fit

The issue of model fit corresponds to the question, how well the actual data fit to a pre-specified model or more technically speaking how close the implied covariance matrix gets to the actual covariance matrix. The question is an inherently statistical one, depending on features of the data, the model, and the estimation method. To illustrate this notion, one should consider that, the more free parameters the model contains, the better the fit will be. This is not surprising since the parameter estimates are derived from the data.

The most common index of fit is the χ^2 goodness-of-fit test, which is directly derived from the value of the fitting function. It equals the product of the value of the fitting function and the sample size minus one. This statistic is χ^2 distributed if the data are multivariate normal and the model is the correct one. These are pretty strict assumptions and particularly the later one might be violated in one or the other instance. The validity of the χ^2 as indicator of model fit has therefore been criticized (Chou, 1995).

The growing dissatisfaction with the χ^2 goodness-of-fit test has led to the development of *adjunct fit indexes.* These indexes are descriptive and often interpreted intuitively. Pioneers in this field of research are Bentler and Bonett (Bentler, 1980), who developed the normed fit index and the nonnormed fit index. These and numerous other fit indexes follow a similar logic: the fit of a specified model is compared to the fit of an independence or null model. A null model is a model in which all relations are fixed at zero and only the variances are estimated. The resulting fit index is thus a measure for the improvement in fit of the specified model compared to the null model.

Adjunct fit indexes are not statistics. This implies that there is no critical value to tell you whether the fit is good or not. Most of the adjunct fit indexes vary between zero and one and an index of 0.9 or larger is widely regarded to indicate that the model is consistent with the observed data. But the number of fit indexes is large, as well as the number of opinions on which to use. The best advice seems to be to use multiple adjunct fit indexes from different classes of indexes to evaluate the goodness of fit.

A somewhat more precise solution for evaluating fit is to compare models. Yet the result you get is which of the compared models fits better to the data and again no statement about an absolute fit. To compare models they have to be nested. That is, they contain the same parameters and the free parameters of one model are a subset of the free parameters of the other model. For both models the χ^2 statistic is calculated. The difference of these two statistics ($\Delta\chi^2$) is then again tested for significant deviation from zero. If $\Delta\chi^2$ differs significantly from zero, then the model with the lower χ^2 fits significantly better to the data than the other one.

6.5 Model modification

A rather controversial aspect within the field of SEM is the notion of model modification or respecification (MacCallum, 1992). Motor for model modifications is usually a not satisfying fit of the model to the data. The aim of the model modification is to improve this fit. This can either be done by freeing formerly fixed parameters or by fixing formerly free parameters. The controversy concentrates not on whether to make model modifications, but rather on the basis for model modification. In comparing SEM to ANOVA model comparison is analogous to planned comparisons, and model modification is analogous to post-hoc comparisons. Model modification strategies do of course lead to loss of control over Type I errror (so-called α-error cumulation). This can lead to a situation in which model modification simply builds idiosyncracies of the data into the model, which might then be misinterpreted as reliable findings (MacCallum, 1992).

Model modification strategies comprises the inspection of estimated parameters, inspection of the residual matrix and tentative stepwise adjustments that might lead to a more favorable fit. State-of-the-art computer programms also provide so-called modification indexes which calculate the gain in $\Delta\chi^2$ for every free parameter if it was subsequently fixed and every fixed parameter if it was freed.

The researcher should always bear in mind that a good fit does not make a good model, unless the a posteriori imposed changes can be justified on theoretical grounds and cross-validated in additional datasets.

6.6 Interpretation

In regard to the research hypothesis the most important issue is that of the interpretation of the results of the structural equation modelling. The first step is the evaluation of the overall fit of the model to the data. If either the χ^2 goodness-of-fit test or adjunct fit indexes indicate acceptable overall fit of a specified model, then the focus moves to specific elements of fit. All free parameters, that have been estimated, can be evaluated against some specified null value, typically zero. To do this the parameter is divided – i. e. standardized – by its standard error. This ratio is z distributed and therefore needs to exceed 1.96 to differ significantly from zero.

Parameters can be presented either in a standardized or in an unstandardized fashion. While the unstandardized parameters retain scaling information, the standardized parameters are free of scaling information. Thus standardized parameters index the number of standard deviations change in the dependent variable per standard deviation change in the independent variable, when all remaining independent variables are at their mean (i. e. at zero). Standardized parameters can therefore be interpreted like effect-size estimates in classical analyses like t-tests and ANOVA.

One essential aspect in interpreting relations between variables in SEM regards the nature of those relations. SEM is often described as a statistical means of testing causal hypotheses from correlational data. Of course, this is not possible for the necessary conditions for demonstrating causality are: association, isolation, and directionality (Bollen, 1989). Association means that the cause and the effect must be related (i. e. correlated). Isolation demands that the relation in question is not due to other causes. To avoid such a confounding by extraneous variables one randomly assigns the subjects or objects under investigation to the levels of the causal variable. Finally directionality has to be proven. This can either be done by logic, theory, or most powerfully, by research design. Directionality cannot be proven on a statistical basis.

6.7 Differences between SEM and standard approaches

First, the use of SEM requires formal specification of a model to be tested and estimated. There is no default model specification like in ANOVA and there are very few limitations on what types of relations can be specified. This fact makes it necessary for the researcher to think very carefully about the data and the hypotheses regarding each variable. Second, and most compelling is the capability of SEM to estimate and test relations between latent variables. This permits to use concepts free of measurement error and uniqueness and increases the probability of detecting associations. The third difference is unfortunately not in favor of SEM. While there is relatively straightforward testing in standard statistical approaches, with results being either significant or not significant, there is nothing like that in SEM. At the heart of this ambiguity is the complex effect of data and model characteristics on the χ^2 statistic on which most indicators of model fit are based. As mentioned earlier in this section the most defensible strategy of evaluating model fit is to use various fit indexes from different classes or types of indexes.

7 Deduction of research objectives and operationalisations

The studies included in this thesis aim at validating the concept of allostatic load for a middle-aged population in the work context. In particular, the first study tries to establish an association between psychosocial factors, subsumed under “environmental stressors” and “perceived stress”, respectively, in McEwen’s model (McEwen, 1998a)(see figue 1, p.10), and physiological parameters contributing to allostatic load. While this research objective addresses a direct influence, the second study investigates the indirect influence, “perceived stress” exerts on the “physiologic responses” via “behavioural responses”.

In order to be able to test these hypotheses, the different concepts were operationalized as follows:

- Allostatic load was assessed using the ten parameters originally used in the MacArthur Studies on Successful Aging (Seeman, McEwen et al., 1997; Seeman, Singer et al., 1997). Additionally, tumor necrosis factor alpha and C-reactive protein were used as indicators of inflammation (Appels, 1999; Cavusoglu et al., 2001; Koenig, 2001; Mendall et al., 2000), urinary albumine and sodium excretion (Alderman, Sealey, Cohen, Madhavan, & Laragh, 1997; Doyle, Chua, Duffy, & Louis, 1975) as indeces for kidney functioning (Gerstein et al., 2001; Turgut, Genc, & Kaptanoglu, 1999), and body mass index as an index of long-term levels of metabolism (Hecker et al., 1999; Lakka et al., 2001). Allostatic load was calculated both as “highest risk” quartiles summary score (Seeman, Singer et al., 1997), and using structural equation modelling as outlined in chapter 6, following more recent considerations by Karlamangla (Karlamangla, unpublished).

- The model component “perceived stress” was measured by Appels’ concept “vital exhaustion”, which has been shown to be a subjective indicator for well-being that predicts objective health outcomes (Appels et al., 1993; Appels, Kop, Bar, de Swart, & Mendes de Leon, 1995; Appels & Mulder, 1988; Appels & Otten, 1992; Kop, 1994; Kop et al., 1994). Additional measures for “perceived stress” include the physical and mental summary scores of the short-form General Health Questionnaire SF-36 (Bullinger & Kirchberger, 1998), and a symptom checklist assessing symptoms typically found in the context of somatisation (Burke, 1999).

- The model component of “environmental stressors”, which can actually not be separated from the notion of “perceived stress”, is restricted to the work context, because the validity of the model for exactly this context is under investigation. For reasons outlined in section 4.3.4, the questionnaire *Salutogenetische Subjektive Arbeitsanalyse* (SALSA)(Rimann, 1997) was chosen to assess psychosocial factors related to work characteristics and social support at work.

- Finally, the component of “behavioural responses” was operationalized by the health-related behaviours smoking, alcohol consumption, and physical activity.

All deductions and operationalisations follow conclusions from the reviewed literature on the respective topics in chapters 2 to 6. Specific details regarding study design, sample, and study procedure can be obtained from the following chapters, which present the two studies mentioned above.

8 Study 1: The association between psychosocial factors and allostatic load in a middle-aged working population

8.1 Abstract

The concept of allostatic load has been introduced as a model referring to the wear and tear the environment exerts on the individual. We set out to establish the link between psychosocial variables and allostatic load in a middle-aged working population. The study population comprised 537 randomly selected employees of an airplane manufacturing plant. Principal component analysis yielded the psychosocial factors “social support at work”, “task properties”, and “perceived well-being”, as well as several first-order health factors, constituting a second-order factor “biological health status”. The three psychosocial factors well-being (β = 0.23), social support at work (β = 0.24), and task properties (β = -0.19) explained 12% of the variance in “biological health status” and 2% of the variance in a simplified allostatic load summary score. The study shows that perceived distress may elicit physiological responses relevant to adverse health outcomes, and it emphasizes the need for an extension of the allostatic load concept beyond a simplified summary score.

8.2 Introduction

Allostatic load has been conceptualized as a measure of the cumulative biological burden of the body’s life long adaptation to external stressors (McEwen & Seeman, 1999; McEwen & Stellar, 1993). The concept aims to operationalize the wear and tear on the organisms’ multiple systems, due to repeated attempts to maintain homeostasis in reaction to environmental challenges. These challenges may include perceived psychosocial stressors arising from work, relationships, as well as health-promoting or health-damaging behaviors including diet, exercise and smoking. To date, the conceptualization of allostatic load has largely been restricted to the elderly. In the MacArthur Successful Aging Study, investigators demonstrated an association between high allostatic load scores and declines in cognitive and physical functioning as well as increased mortality at a 7-year follow-up (Seeman et al., 2001; Seeman, Singer et al., 1997).

In this study, the allostatic load measure comprised 10 variables: systolic and diastolic blood pressure, waist to hip ratio, total cholesterol to HDL ratio, LDL, DHEA-S, glycosylated hemoglobin and urinary cortisol, epinephrine and norepinephrine. One point was assigned for each value lying in the highest-risk quartile of a particular measure. Points were added up to an allostatic load score. In an attempt to broaden the concept, it was suggested to include markers of immune function and of inflammatory and hemostatic activity as well (Seeman et al., 2001). Acknowledging the multifactorial nature of allostatic load, alternative mathematical models have been explored, such as canonical correlation analyses to derive weighting systems (Karlamangla et al., unpublished).

It is elusive, whether the association of high allostatic load scores and poor health outcomes is reproducible in younger populations who are the primary target of preventive health interventions.

We have designed a prospective cohort study to investigate the allostatic load concept in stress-exposed employees of the airplane manufacturing industry. The main goal of that longitudinal study is to test for the validity of the allostatic load concept as an early warning system of biological markers in working populations (similar to the approach of the Framingham algorithm that calculates cardiovascular risk)(Lenfant, Friedman, & Thom, 1998; Sytkowski, D'Agostino, Belanger, & Kannel, 1996). In the present cross-sectional analysis of the data at study entry, we had two aims: 1) To establish an association between adverse or protective psychosocial variables and measures of allostatic load. 2) To test for the adequacy of various models for operationalizing “biological health” as measured by allostatic load.

Faced with the task to choose additional parameters for the extension of allostatic load in a working population, we restricted our selection on factors predictive for cardiovascular disease. The added markers covered inflammatory activity (high sensitivity C-reactive protein and tumor-necrosis factor alpha) (Appels, 1999; Koenig et al., 1999; Lindahl et al., 2000; Mendall et al., 2000; Ridker et al., 2000), sub-clinical renal dysfunction (microalbuminuria and sodium excretion)(Gerstein et al., 2001; Jensen et al., 2000) and body mass index (Hecker et al., 1999; Lakka et al., 2001).

While an allostatic load summary score may relate to long-term health outcome, the relationships between external stressors and allostatic load variables may be more complex. To investigate the latter, we employed structural equation modeling. Physiological parameters were related to existing physiological or regulatory pathways constituting primary or first order factors. We modeled biological health as an error-free second order factor, determined by these primary factors. In a final step, we investigated the effect of adverse and protective psychosocial work characteristics on this biological health factor. We modeled psychosocial stressors from work characteristics (social support at work, task properties), and from subjective measures of health perception (e. g. exhaustion) previously related to increased cardiovascular disease risk (Appels, 1990; Appels et al., 1993; Appels et al., 2000; Appels & Mulder, 1989; Kop et al., 1996; Kop et al., 1994).

8.3 Method

8.3.1 Participants

Data were collected from a stratified random sample of employees (647 of 1760) at an airplane part and assembly manufacturing plant in Germany. Of the potentially eligible subjects, 537 (83%) participated in the questionnaire examination of psychosocial variables. All participants were offered a consecutive medical examination, which 332 agreed to undergo (324 complete datasets).

8.3.2 Measures

8.3.2.1 Psychosocial variables

Perceived well-being, task properties and social support at work were assessed. Perceived well-being was measured using three questionnaires: (1) General health was assessed by the German version of the SF-12, a short version of the SF-36 Questionnaire (Bullinger et al., 1998; Bullinger & Kirchberger, 1998). The questionnaire provides a physical and a mental health summary score. (2) Exhaustion was measured using the short version of the Maastricht Questionnaire (Appels, Hoppener, & Mulder, 1987). (3) Subjective health complaints were assessed by a 20-item symptom checklist (Burke, 1999).

Task properties and social support at work were determined by the questionnaire Salutogenetische Subjektive Arbeitsanalyse (SALSA), an instrument designed for the assessment of pathogenic as well as salutogenic working conditions (Rimann, 1997). The sub-scales "responsibility and required qualification demands", "qualification potential", "task variety", "decision authority", "social support by coworker", "supportive supervisor behavior", "adverse coworker behavior" and "adverse supervisor behavior" were used.

8.3.2.2 Physiological variables

For determination of the physiological parameters, we followed the laboratory procedures as outlined by the MacArthur study group in their original definition of the allostatic load score (Seeman, Singer et al., 1997). The score was calculated from plasma levels of DHEA-S, HbA_{1C}, LDL, HDL, and cholesterol, from overnight urinary excretion of norepinephrine, epinephrine, dopamine, and cortisol as well as from waist-to-hip-ratio, systolic and diastolic blood pressure (Seeman, Singer et al., 1997). Overnight urine sampling started at 10 p.m.. Blood samples were obtained after awakening and prior to a morning working shift. Serum samples (HDL, LDL, cholesterol, DHEA-S), urinary specimens (cortisol, albumin, sodium, catecholamines), and glycosilated hemoglobin were analyzed according to standard laboratory protocols.

High sensitivity C-reactive protein was measured by immunoassay (Immunolite, DPC Biermann, Germany). Tumor necrosis factor-a was determined from citrate plasma by means of a high sensitivity immunoabsorbent assay (R&D Systems, Minneapolis, MN, USA) with special precaution (precooled tubes) to avoid post-collection liberation of the cytokine. All subjects had their weight and height measured to compute body mass index.

8.3.3 Study Procedure

Subjects completed questionnaires and medical examination during working hours. Participation time was recorded as working time. No further incentives were offered. Questionnaires were completed during one-hour group sessions (12 to 15 participants) after standardized introduction. All questionnaire data were obtained within five days. After completion of the questionnaires, subjects who participated in the medical examination had a 15-minute resting period before blood pressure was determined. Blood sampling was scheduled between 8 and 10 a. m. within the following 20 days prior to a morning shift and following a night, the participant was not on duty. Subjects collected overnight urine during the night before blood sampling.

8.3.4 Statistical Analysis

First we performed an exploratory principal component analysis examining the factorial structure of the collected data. The oblimin-rotated solution of this principal component analysis served as a scaffolding for the measurement model of the subsequent structural equation modelling. Factors were named with regard to their highly loading indicators.

In a second step the revealed factors were combined in the structure model part of the structural equation model following the theoretical considerations outlined in the introduction. We then tested, whether the data fit this model. A maximum likelihood algorithm was applied, also estimating means and intercepts due to missing values. Missing values were treated using the full information maximum likelihood. This method has been shown to minimize distortion of the original distribution of the data (Arbuckle, 1996). We compared this model to the fit of the data to a simplified model in which we omitted first and second order factors for physiological variables, and in which we substituted the second order factor “Biological Health” by the summary score for allostatic load (Seeman, Singer et al., 1997). We computed these analyses using AMOS (version 4.0, Smallwaters Corp., Chicago, Illinois, USA), all other calculations were carried out using SPSS (version 10.0, Inc. Chicago, Illinois, USA).

8.4 Results

8.4.1 Participants and measurements

Table 1 presents the baseline characteristics for all participants and for the subset of subjects who underwent medical examination. The table also shows the mean and the distribution of the physiological and psychosocial measurements.

8.4.2 Principal Component Analysis

The factor scree plot suggested 8 factors, which were also the factors with an eigenvalue larger than 1. The oblimin-rotated solution yielded the loadings presented in Table 2. With few exceptions, Table 2 reveals a simple structure in the factor loadings with either very high loadings or very low loadings. The two noteworthy exceptions were the variables "cortisol" and "blood pressure". These two variables showed high loadings on two factors. The variables tumor necrosis factor–a, urinary albumin and urinary epinephrine excretion failed to load highly on any of these eight factors and were therefore not included in the subsequent structural equation model.

With regard to the respective highly loading indicators, the factors were named as follows (factor numbering with reference to Table 2):

Factor 1: "Task Properties"; factor 2: "Social Support at Work"; factor 3: "Perceived Well-Being"; factor 4: "Urinary Excretion"; factor 5: "Body constitution"; factor 6: "Fat Metabolism"; factor 7: "Ageing"; and factor 8: "Inflammation". The combination of these factors into the structure model is shown in figure 5.

Table 1. Characteristics of the two subsamples.

	Participants (questionnaires plus medical examination)	Participants (questionnaires only)
Number	324	213
	Mean (SD)	Mean (SD)
Age in years	40.6 (±9.3)	39.2 (±11.5)
Responsibility and required qualification demands	16.5 (±2.8)	16.1 (±3.0)
Qualification potential	10.1 (±2.8)	9.8 (±2.8)
Task Variety	10.3 (±3.1)	10.0 (±3.1)
Decision Authority	10.3 (±2.8)	9.8 (±2.7)
Social Support by Coworker	14.1 (±2.9)	13.7 (±3.0)
Supportive Supervisor Behavior	15.4 (±4.4)	15.2 (±4.3)
Adverse Coworker Behavior	7.6 (±2.2)	7.2 (±2.1)
Adverse Supervisor Behavior	6.4 (±2.6)	6.6 (±2.9)
Vital Exhaustion	7.2 (±5.0)	5.7 (±4.9)
SF12 – Mental Summary Score	49.0 (±9.0)	50.5 (±8.9)
SF12 – Physical Summary Score	49.2 (±7.6)	50.4 (±6.4)
Symptom Checklist	5.4 (±3.8)	4.8 (±4.0)
Cholesterol (mg/dl)	221.5 (±41.2)	/
HDL (mg/dl)	44.3 (±11.4)	/
LDL (mg/dl)	121.0 (±31.3)	/
HbA1C (%)	5.18 (±0.51)	/
C-reactive protein (mg/l)	2.1 (±3.7)	/
Urinary epinephrine (nmol/l)	6.1 (±11.3)	/
Urinary norepinephrine (nmol/l)	139 (±108)	/
Urinary dopamine (nmol/l)	1366 (±712)	/
TNF-α (pg/ml)	1.9 (±1.5)	/
DHEA-s (μg/l)	2933 (±1482)	/
Urinary sodium (mmol/l)	112.9 (±55.5)	/
Urinary albumin (mg/l)	3.9 (±7.8)	/
Body-Mass-Index	26.5 (±3.9)	/
Waist-to-Hip-Ratio	0.92 (±0.073)	/

SD = standard deviation

Table 2. First order factors with highly loading variables.

	1	2	3	4	5	6	7	8
Responsibility and required Qualification Demands	**-.76**	.17	-.05	.05	-.07	-.03	.15	.10
Task Variety	**-.84**	.24	-.23	-.07	.00	.01	.02	.05
Qualification Potential	**-.82**	.35	-.33	.01	.04	-.06	-.03	.05
Decision Latitude	**-.72**	.26	-.12	.06	-.01	.08	.24	-.19
Adverse Coworker Behavior	.12	**-.73**	.37	-.09	-.12	.04	-.11	-.22
Adverse Supervisor Behavior	.23	**-.80**	.21	.09	-.03	.07	-.09	.04
Social Support by Coworker	-.21	**.68**	-.23	.06	.02	-.11	-.05	.32
Supportive Supervisor Behavior	-.40	**.79**	-.25	-.07	.01	-.01	-.03	-.07
Vital Exhaustion	-.04	-.29	**.90**	-.13	-.09	.11	.12	-.04
SF12 – Mental Summary Score	-.19	.31	**-.84**	.09	-.01	-.08	.01	.11
Symptom Checklist	.21	-.22	**.82**	-.09	-.12	.04	.19	.07
Dopamine	.00	-.01	-.13	**.87**	-.01	-.13	-.18	-.10
Norepinephrine	-.04	.00	-.11	**.80**	.01	-.08	-.03	-.05
Sodium	.03	-.03	-.08	**.63**	-.15	-.17	.07	.04
HDL	.02	.01	-.02	.00	**.69**	.09	.24	.03
Waist-to-Hip-Ratio	.00	-.08	.09	.07	**-.75**	.21	.11	-.12
Body-Mass-Index	-.01	-.08	.09	.08	**-.76**	.06	.36	-.01
Cholesterol	.03	-.10	.10	-.17	-.07	**.96**	.14	-.06
LDL	.02	-.06	.10	-.16	-.07	**.95**	.07	-.07
DHEA-S	.05	-.08	-.11	.11	-.05	.01	**-.75**	.00
Age	-.28	.03	.15	-.03	-.26	.33	**.78**	-.02
Mean Blood Pressure	-.16	-.13	.02	.15	**-.51**	.33	**.48**	.11
C-reactive protein	.08	-.13	.10	-.07	-.19	.08	.05	**-.81**
Cortisol	-.06	-.14	-.09	**.48**	.10	.06	-.07	**-.68**

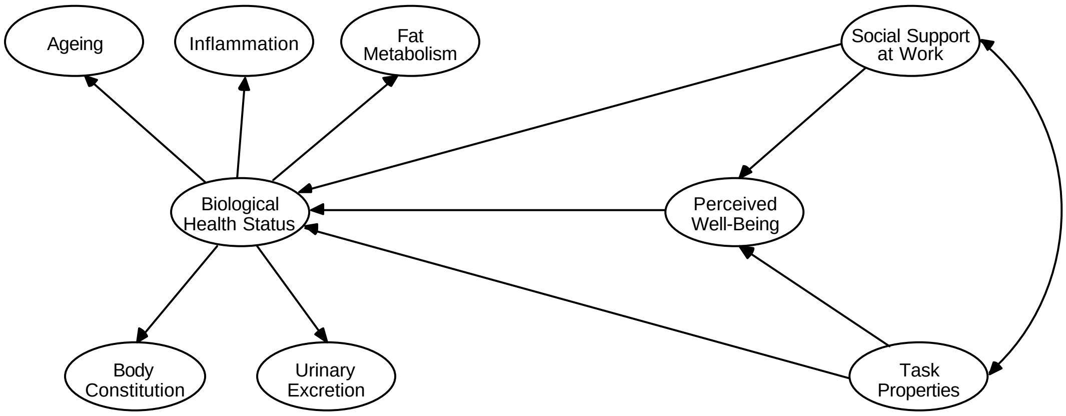

Figure 5: Theoretical model of the relations between the factors derived from the principal component analysis (see table 2). Single-headed arrows denote regression coefficients. The double-headed arrow indicates a correlation.

8.4.3 Structural Equation Modeling

(a) The complete model - including measurement and structure model - that was tested in the subsequent analysis is shown in figure 6.

Model fit: The model contained 23 observed and 39 unobserved variables, 299 distinct sample moments and 80 distinct parameters to be estimated, resulting in 219 degrees of freedom. The minimization converged at a Chi-square of 585.82 which compares to a probability level of $P < 0.001$. The Chi-square/df ratio was 2.67 . The goodness of fit indices were: NFI = 0.979, IFI = 0.986, CFI = 0.986, Hoelter (0.5) = 246, Hoelter (0.1) = 261. The RMSEA was 0.054 (p_{close} = 0.083) indicating reasonably good fit of the model to the data

(Hoyle, 1995). The well-established goodness of fit indices GFI and AGFI are not defined for missing data and could therefore not be calculated.

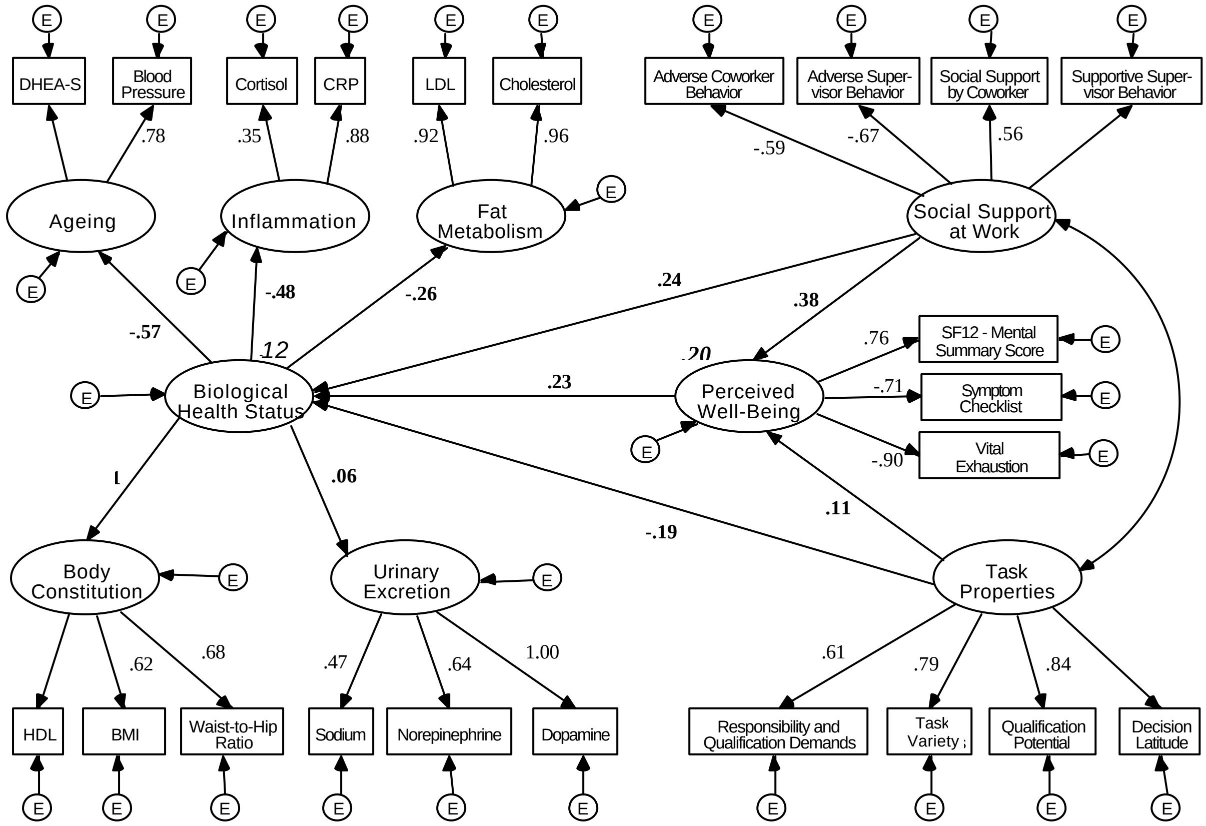

Figure 6: Fit of the cross-sectional data of 537 employees in the airplane manufacturing industry to the structural equation model. E denotes error terms, rectangular boxes indicate measurements, ellipses represent latent factors. Numbers are standardized regression coefficients (single-headed arrows). The double-headed arrow indicates a correlation. The italic numbers indicate squared multiple correlations (explained variances). In this model, 12% of the variance in “Biological Health Status” are explained by the three factors “Social Support at Work”, “Perceived Well-being” and “Task Properties”. Together, “Social Support at Work” and “Task Properties” explained 20% of the variance in “Perceived Well-being”.

First order factors: In principle, testing of the model confirmed the factors of the principal component analysis. The factors “Task Properties”, “Social Support at Work”, “Perceived Well-Being”, “Urinary Excretion”, “Body Constitution” and “Fat Metabolism” could well be established. The construction of the factors “Ageing” and “Inflammation” is slightly weaker. Figure 6 displays the loadings of each variable on the latent first order factors. Except for DHEA-S all loadings on the first order factors differed significantly from zero ($p \leq 0.05$).

The second order factor: The second order health factor was contributed to by the first order factors “Ageing” (ß = -0.57), “Inflammation” (ß = -0.48), “Fat Metabolism” (ß = -0.26), “Body Constitution” (ß = -0.71), and to a negligible degree by “Urinary Excretion” (ß = 0.06). Except for “Urinary Excretion”, all loadings of the first order factors on the second order factor were significant ($p \leq 0.05$).

Relationships between factors: The factors “Social Support at Work” and “Task Properties” are correlated at 0.51 ($p < 0.05$) . “Social Support at Work” influences “Perceived Well-being” at ß = 0.38 ($p < 0.05$) and “Biological Health Status” at ß = .24 ($p < 0.07$) , while “Task Properties” influences “Perceived Well-being” at ß = 0.11 ($p < 0.08$) and “Biological Health Status” at ß = -0.19 ($p < 0.09$) . The influence of “Perceived Well-being” on “Biological Health Status” is ß = 0.23 ($p \leq 0.05$) . These effects add up to explain 20% of the variance in “Perceived Well-being” and 12.4% of the variance in “Biological Health Status”.

(b) Comparison with a simplified model: In this analysis, the second order factor “Biological Health Status” was substituted by the allostatic load summary score. In addition, all individual physiological measures and the related first order factors were omitted.

Model fit: The model contained 12 observed and 16 unobserved variables, 90 distinct sample moments and 41 distinct parameters to be estimated, resulting in 49 degrees of freedom. The minimization converged at a Chi-square of 435.53 which compares to a probability level of

$P < 0.001$. The Chi-square/df ratio was 8.88 . The goodness of fit indices were: NFI = 0.974, IFI = 0.977, CFI = 0.977, Hoelter (0.5) = 87, Hoelter (0.1) = 98. The RMSEA was 0.118 ($p_{close} < 0.001$) indicating a poor model fit.

Model details: Although the overall model fit is rather poor, the factors “Task Properties”, “Social Support at Work” and “Perceived Well-Being” could well be established. All loadings on these factors differed significantly from zero ($p \leq 0.05$). Except for “Social Support at Work”, the influences of the above factors on the allostatic load summary score did not reach significance. The variance in the allostatic load summary score, explained for by the psychosocial factors, was 2%.

8.5 Discussion

In this study we wanted to show, that complex modelling may reveal substantial associations between psychosocial variables and biological risk factors for adverse health outcomes (i. e. cardiovascular disease). We further were interested in the extent to which these associations were quantifiable in a working population. We fitted psychosocial and medical data from a population of industrial employees across two structural equation models. One model contained an extended allostatic load summary score, the other one employed a construct of first-order factors and a single second-order factor to represent “Biological Health Status”. While psychosocial variables could only explain 2% of the variance in the allostatic load summary score in a model with poor overall fit, we showed that the same psychosocial variables explained 12% of the variance in a measurement error free second order factor “Biological Health Status. For all of the applicable measures, this model obtained reasonably high goodness of fit indices.

The reasonable fit of the data allows to interpret the significant relations within the model. The parameters representing allostatic load yielded high loadings in the factor analysis and related to the first order factors representing physiological systems. Of these first order factors, “Inflammation ” (cortisol, CRP), “Body Constitution” (HDL, body-mass index, waist-to-hip ratio) and “Ageing” (DHEA-S, mean blood pressure) contributed strongly to the second order factor “Biological Health Status”. The first order factor “Fat Metabolism” (cholesterol, LDL) had lesser but still substantial influence, while the relation of the factor “Urinary excretion” (sodium excretion, urinary dopamine and norepinephrine) was not significant.

Our model provides a structure for describing the relation between individual psychosocial variables and “Biological Health Status”. The factor analysis revealed three first order factors, namely “Social Support at Work”, “Task Properties” and “Perceived Well-being”. The strongest influence on “Biological Health Status” was exerted from “Social Support at Work” both by a direct influence and, indirectly, by increasing „Perceived Well-being", the latter being related to a similarly high degree to "Biological Health". Similar findings have been reported in numerous studies concerning cardiovascular disease (CVD), pointing out that reduced social support is associated with negative health outcomes (Hemingway & Marmot, 1999).

Rather unexpectedly, we found that highly desirable task properties such as higher levels of responsibility, task variety and qualification potential were negatively related to "Biological Health", although they were positively related with "Perceived Well-being". Even though we acknowledge that there were trends only for these observations, they stand in contrast to findings from previous studies reporting a beneficial cardiovascular effect of desirable task properties (Haan, 1988; Lacroix, 1984). Nonetheless, increased risk for coronary heart disease has also been related to higher job variety (Netterstrom & Suadicani, 1993), which is one of the indicators of our "Task Properties" factor. In our study population, individuals who had high levels of job latitude, task variety and qualification potential were mostly foreman and middle management. These employees carry the main responsibility for productivity, and often they work overtime. We speculate that these employees may indeed report higher levels of perceived well-being, although the burden of chronic stress exerted an unfavourable influence on objective intermediate health measures. Unfortunately, the limited number of subjects in this category prevented from performing a valid subgroup equation model.

Our finding that "Perceived Well-Being" exerts a positive influence on "Biological Health Status" is consistent with other studies in the field. For example, the highest-loading indicator of "Perceived Well-Being", vital exhaustion, has repeatedly been shown to be related to myocardial infarction (Appels, 1990; Appels et al., 2000; Appels & Mulder, 1988, 1989; Kop et al., 1996; Kop et al., 1994).

Our study has several limitations. First, it would have been desirable to include additional measures of health behavior into the model such as smoking, alcohol consumption, and physical activity, though the sample size precluded extension of the model. Second, we were unable to study influences of sex, because females represented less than an eighth of the study population. Third, there is considerable dispute on the interpretation of cross-sectional data. However, we will follow-up our study population in terms of longitudinal health outcomes to validate the model.

In conclusion, we showed that psychosocial variables are able to explain a considerable amount of the variance in “Biological Health Status”, constructed from risk factors of the extended allostatic load concept, while there was little association between these psychosocial variables and the allostatic load summary score. Our findings support the hypothesized association between perceived stress and physiologic responses (McEwen & Stellar, 1993) related to cardiovascular disease and increased mortality. Furthermore, they support recent efforts to extend the measurement of allostatic load by including additional parameters and beyond a simplified summary score (Seeman et al., 2001)(Karlamangla et al., unpublished). Our findings add credibility to the allostatic load concept and its applicability to middle-aged working populations.

9 Study 2: Association of job characteristics and subjective well-being with lifestyle risk factors for coronary artery disease in healthy industrial employees

9.1 Abstract

Objective: To elucidate whether psychosocial conditions at work exert their influence on coronary artery disease (CAD) independently or by modifying health behavior.

Design: Cross-sectional study.

Methods: Three major psychosocial factors, namely “task properties”, “social support at work” and “subjective well-being” were used in regression analyses to predict scores in the lifestyle variables smoking, alcohol intake and physical activity in 403 healthy industrial employees.

Results: Controlling for age, sex, job status, mean blood pressure, LDL/HDL ratio and levels of HbA1c, “task properties” was modestly associated with the average number of cigarettes smoked per day, while “subjective well-being” was modestly associated with physical activity. “Social support” showed no significant association with any of the three lifestyle variables.

Conclusion: The relations between the psychosocial and the lifestyle variables were modest at best. Our data support the notion that the psychosocial variables may exert their cardiovascular threat mostly independently from the health behavior.

9.2 Introduction

Coronary artery disease (CAD) is the leading cause of death in men 50 years and older, and in women after menopause (Grodstein, Manson, & Stampfer, 2001), most of whom still are in their working life. Large epidemiological studies have shown that lifestyle risk factors contribute to CAD. In men smoking is one of the three major risk factors (besides blood pressure and serum lipids) (Stamler et al., 1999). Other lifestyle factors, in particular physical activity and low to moderate alcohol intake, exert protective influences on coronary arteries, while high levels of alcohol intake increase the risk for coronary fatalities (Smith, Shipley, Batty, Morris, & Marmot, 2000) (Klatsky, Armstrong, & Friedman, 1990). The reported risk ratios for smoking related CAD mortality exceed those attributed to biological risk factors such as high cholesterol levels (Stampfer, Hu, Manson, Rimm, & Willett, 2000) (Stamler et al., 2000).

In addition, prospective studies have found that adverse work conditions (i.e., job stress) and lack of social support both predict increased rates of coronary events in apparently healthy middle-aged populations (Kaplan & Keil, 1993) (Tennant, 2000). The links between adverse psychosocial factors, perceived stress levels, and poor health outcome are not fully understood (Belkic et al., 2000). Some authors have favored pathways, which consider acute and chronic changes in the functioning of psycho-neuro-endocrine regulatory circuits (Belkic et al., 2000). According to the concept of allostasis and allostatic load, sustained psychosocial distress may exaggerate sympathetic nervous system activity and adrenal hormone secretion, with unfavorable effects on regulated physiological systems downstream (McEwen & Seeman, 1999). The proponents of the allostatic load concept have also pointed out an alternative pathway, namely wear and tear on the regulatory systems as a consequence of adverse lifestyle and health (Seeman et al., 2001).

There is much reason to assume that psychosocial conditions may exert their adverse effect on cardiovascular health by modifying health behavior (Belkic et al., 2000). By means of coping with relatively higher levels of perceived distress, such individuals might smoke more, might drink more alcohol, and might refrain from regular physical exercise rather than subjects who perceive themselves as being less distressed (Steptoe et al., 1998; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996).

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If this hypothesis holds true, individuals sharing a common social environment should show differential distributions of adverse lifestyle factors across the spectrum of psychosocial variables. Therefore, we studied potential associations between self-reported health behavior and subjective well-being, task properties and social support at work in a representative sample of Bavarian industrial employees. This sector of the German society is considerably homogenous in terms of other important determinants of health (access to health care, socioeconomic status).

9.3 Methods

9.3.1 Participants

Participants were recruited from a stratified random sample of employees from a manufacturing plant in Germany. This population also served as base for the Augsburg MONICA cohort study on cardiovascular risk factors (Koenig et al., 1999). By March 2001, 628 of the 1760 employees had completed the questionnaires, which assessed psychosocial variables. The majority of subjects (n = 532) were enrolled when the cohort study began in July 2000; the remainder were accrued from ongoing recruitment to the cohort. Of the 628 individuals who were also offered a medical examination including a history, and a questionnaire on lifestyle variables and health-related behavior, 403 participants agreed to participate.

9.3.2 Study Procedure

Participants completed the psychosocial questionnaire package in groups of 12 to 15 persons during their working hours. The time to participate in the study was recorded as working time, but no further incentive was offered. After completion of the questionnaires, participants who agreed to take part in subsequent examinations proceeded to the company physician's practice. At arrival, they completed lifestyle and medical history questionnaires and underwent a medical examination including blood pressure readings. Measures in terms of physical activity, alcohol intake and smoking were derived from the lifestyle questionnaire. The control variables for fastening LDL/HDL ratio and HbA1c were determined from blood collected the following morning.

9.3.3 Measures

Sociodemographic variables included in the calculations comprised age, sex, and job status. The latter served as a proxy for socio-economic status by using the five distinct categories “manager”, “foreman”, “skilled worker”, “unskilled worker” and “apprentice”.

We assessed work characteristics and social support at work using the Salutogenic Subjective Work Analysis (SALSA) by Rimann and Udris (Rimann, 1997). This particular questionnaire has been developed and validated in the southern parts of Germany. Conceptually this questionnaire extends the Karasek-Theorell model on job strain (Karasek, 1990) by focusing on pathogenic as well as salutogenic work characteristics. In the present analysis, we used the SALSA subscales “responsibility and required qualification demands”, “qualification potential”, “task variety”, “decision latitude”, “social support by coworker”, “supportive supervisor behavior”, “adverse coworker behavior” and “adverse supervisor behavior”.

Self-reported well-being was assessed using three different questionnaires: (1) The German version of the SF-12 (Bullinger & Kirchberger, 1998) that is a short version of the SF-36 Health Survey questionnaire (Ware, 1993); it measures general health and provides a physical and a mental summary score of which only the latter was used. (2) Vital exhaustion was measured using the short version of the Maastricht Questionnaire (Appels et al., 1987). (3) Subjective health complaints were assessed by a German version of a 20-item symptom checklist as introduced by Burke et al (Burke, 1999).

The lifestyle variables were by subjects’ self-report, and defined as follows: (1) The variable “smoking” referred to the average number of cigarettes smoked per day, a package being converted into 20 cigarettes; (2) Data on alcohol consumption were obtained using the health behavior questions of the Nurses Health Study (Michaud, Giovannucci, Willett, Colditz, & Fuchs, 2001). The daily average of units of four alcoholic beverage categories consumed (i.e., beer, red wine, white wine, spirits) were expressed as grams of alcohol consumed per day forming the variable “alcohol intake”; (3) Physical activity was also assessed by use of the questions and scoring methods applied in the Nurses Health Study (Hu et al., 2000). Participants had to rate the average time they committed themselves to certain physical activities within a one-week period. The list of 11 categories of activities contained jogging, bicycling and swimming amongst others. The various activities were weighted according to their strenuousness (e. g. walking to work gets a lower weight than playing squash, because the former is less strenuous). “Physical activity” was calculated as the body weight independent energy equivalent.

9.3.4 Statistical Analysis

First, a principal component analysis was carried out to gain factor scores in terms of the hypothesized latent psychosocial constructs. “Responsibility and qualification demands”, “qualification potential”, “task variety” and “decision authority” were hypothesized to make up for a “task properties” factor. “Social support by coworker”, “supportive supervisor behavior”, “adverse coworker behavior” and “adverse supervisor behavior” were hypothesized to build a “social support at work” factor. The scores of the SF12 mental summary subscale, of the symptom checklist, and of the “vital exhaustion” questionnaire were hypothesized to load highly on a factor called “subjective well-being”. Missing values were excluded listwise to prevent distorted distributions.

To test the influence of psychosocial variables on the lifestyle variables smoking, alcohol intake and physical activity, regression analyses were calculated. Across the different analyses, each of the lifestyle variables served as the dependent variable. The three constructs “task properties”, “social support at work” and “subjective well-being” were entered into the regression equation as the independent variables. Furthermore, age, sex, job status, mean blood pressure, LDL/HDL ratio and levels of HbA_{1c} were introduced into the regression as controlling variables. Calculations were by use of the backward elimination technique. We performed separate analysis including all participants and excluding those with positive history (n = 65) for hypertension, atherosclerotic disease, diabetes and / or hyperlipidemia.

For residual analyses of the regression analyses Q-Q-plots were produced to check normality. For those analyses with non-normal residuals, logarithmic and square-root-transformations of the target-variables were calculated to gain normality for the residuals.

In addition to regression analyses we also looked for differences between smokers/non-smokers and subjects reporting regular alcohol intake and those reporting to be abstinent, respectively, concerning their scores on the psychosocial factors. For this purpose Mann-Whitney U-tests were calculated. SPSS (version 10.1, SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. Because we pre-specified the hypothesized direction of the investigated associations (e.g. adverse task properties lead to higher numbers of cigarettes smoked within smokers), all testing was one-tailed with the level of significance set at $p < .05$.

9.4 Results

9.4.1 Participants and measurements

Table 3 shows the baseline characteristics of the random sample of employees, stratified by those who participated in the medical examination and completed lifestyle questionnaires (n = 403), and those who did not agree to have their lifestyle variables assessed (n = 225).

Table 3. Characteristics of the study population.

	Participants (psychosocial and lifestyle variables)	Participants (only psychosocial variables)
Number	403	225
Sex (% female)	13.1	9.3
Status (number)		
Manager	26	11
Foreman	67	32
Skilled worker	288	156
Unskilled worker	22	10
Apprentice	/	16
	Mean (SD)	Mean (SD)
Age in years	40.5 (9.5)	39.1 (11.5)
Responsibility and Required Qualification Demands	16.4 (2.9)	16.1 (3.0)
Qualification Potential	10.0 (2.7)	10.0 (2.8)
Task Variety	10.3 (3.1)	10.0 (3.1)
Decision Authority	10.3 (2.8)	9.7 (2.7)
Social Support by Coworker	13.8 (2.9)	13.7 (3.1)
Supportive Supervisor Behavior	15.2 (4.3)	15.2 (4.3)
Adverse Coworker Behavior	7.7 (2.2)	7.2 (2.1)
Adverse Supervisor Behavior	6.4 (2.6)	6.6 (2.9)
Vital Exhaustion	7.2 (5.0)	5.7 (4.9)
SF12 – Mental Summary Score	48.8 (9.3)	50.5 (9.0)
Symptom Checklist	5.4 (3.8)	4.8 (4.0)
	Median (IQR)	
Smoking (cig/day)	0 (0; 10)	/
Alcohol Intake (g/day)	10.4 (2.6; 21.1)	/
Physical Activity (energy units/week)	4.7 (2.0; 8.1)	/

SD = Standard Deviation; IQR = Inter-Quartile Range

9.4.2 Principal component analyses

The scree plot and the Kaiser criterion suggested extracting three factors with Eigenvalues larger than one. The initial solution was then Varimax rotated and yielded a good simple structure with the observed variables loading highly on one factor ($|r| > .70$) and loading low on the two other factors ($|r| < .27$ apart from one exception of $r = .37$).

Each of the extracted three factors accounted for more than 20% of the variance in the observed variables, making up for a total of 65% of the variance explained for. With regard to the contents, the hypothesized factors could be established very well with high loadings from the hypothesized indicators. The exact factor loadings of the observed variables on the three factors are shown in table 4.

Table 4. Factor loadings

	Factor I "Task Properties"	**Factor II "Subjective Well-Being"**	**Factor III "Social Support at Work"**
Responsibility and required qualification demands	**.75**	-.05	11
Task variety	**.84**	.16	.05
Qualification potential	**.79**	.26	.18
Decision authority	**.72**	.01	.16
Symptom checklist	-.15	**-.81**	-.09
Vital exhaustion	-.04	**-.90**	-.17
SF12 – Mental summary score	.07	**.80**	.20
Adverse coworker behavior	.00	-.20	**-.76**
Adverse supervisor behavior	-.21	-.07	**-.73**
Social support by coworker	.05	.14	**.71**
Supportive supervisor behavior	.37	.11	**.71**

9.4.3 Regression analyses and Mann-Whitney U-tests

Smoking as the dependent variable: The Mann-Whitney U-test for differences between the groups of smokers (≥ 1 cigarette per day) and non-smokers was significant for the "task properties"-factor ($p <= 0.05$). Smokers showed lower values for "task properties" than non-smokers. Figure 7 shows the difference between non-smokers, moderate and excessive smokers. Regression analysis was carried out for smokers, adjusting for HDL/LDL ratio, mean blood pressure, and HbA1c levels. Participants with a positive history for the above mentioned diseases were excluded from this analysis. With smoking as the dependent variable, the residuals showed the best approximation to normality for the logarithmic transformation. Using the backward elimination algorithm the only significant model comprised "task properties" alone as the independent variable (adjusted $R^2 = 0.05$, $\beta = -0.21$, $p = 0.04$). Note that higher scores on the "task property" factor indicate more favorable work conditions. Repeating the analysis on all smokers, and omitting adjustment for risk factors, did not change the direction of the association ($R^2 = 0.06$, $\beta = -0.26$, $p = 0.0085$).

Alcohol intake as the dependent variable: The regression analysis with alcohol intake as the dependent variable yielded the best approximation to normality for the residuals for the square-root transformation of the target variable. The analysis was carried out for all individuals (data not shown), and after excluding participants with history of hypertension, atherosclerotic disease, diabetes and / or hyperlipidemia and adjusting for the risk factors HbA1c, mean blood pressure and HDL/LDL ratio. Following the backward elimination algorithm several regression models were significant (all at $p < 0.001$). The first-choice model had an adjusted R^2 of 0.20 and contained age ($\beta = 0.35$), sex ($\beta = 0.27$, females coded as 0), and subjective well-being ($\beta = -0.11$). Participants aged 40 years or younger reported a median alcohol intake of 9.7 g/day, while those aged older than 40 years reported a median alcohol intake of 12.6 g/day. The Mann-Whitney U-test for differences between the groups of individuals reporting alcohol intake and those reporting abstinence was not significant for any of the psychosocial factors.

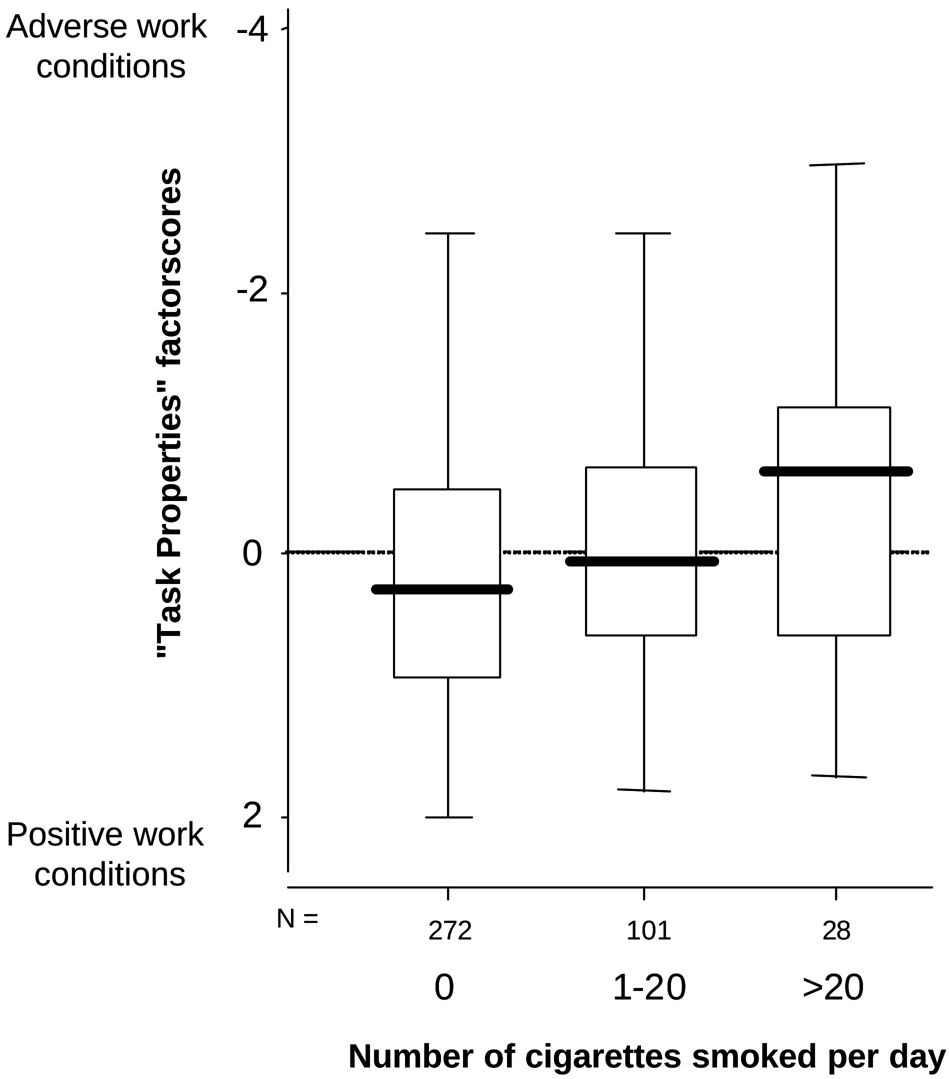

Figure 7. Task property scores in relation to self-reported number of cigarettes smoked per day. Negative scores on the factor "task properties" indicate lower self-reported perception on the subscales for responsibility and required qualification demands, task variety, qualification potential and decision authority.

Physical activity as the dependent variable: The regression analysis with physical activity as the dependent variable also yielded the best approximation to normality for the residuals for the square-root transformation of the target variable. The analysis was carried out using the same exclusion and adjustment criteria as above. When following the backward elimination algorithm, only one regression model was significant at $p = 0.038$. The adjusted R^2 being 0.01. The only significant independent variable was “subjective well-being” with $\beta = 0.12$. Because the questionnaire also included regular non-recreational physical activity, e.g. walking to work, there were no individuals with zero physical activity, and therefore, we refrained from group comparison.

9.5 Discussion

In this study, we tested the hypotheses of an association between self-reported lifestyle variables and subjective perception of well-being, health and work characteristics in a middle-aged cohort of industrial employees The psychosocial variables were operationalized as “subjective well-being”, “task properties” and “social support at work”. Similar construct variables have been predictive for coronary events (Barefoot et al., 2000) (Greenwood, Muir, Packham, & Madeley, 1996) (Peter & Siegrist, 2000). The lifestyle variables consistently related to CAD assessed were smoking, alcohol intake and physical activity ("27th Bethesda Conference. Matching the Intensity of Risk Factor Management with the Hazard for Coronary Disease Events. September 14-15, 1995," 1996). Our main findings suggest that employees who scored high in “task properties” smoked relatively less, and that those workers who scored high on “subjective well-being” were relatively more physically active. Of note, results remained significant when age, gender, job status, mean blood pressure, LDL/HDL ratio and levels of HbA_{1c} had been controlled for, suggesting quite robust associations across different job profiles, ages, and men and women. Nonetheless, while these findings were in the expected direction, they were unexpectedly weak on the other hand with only a few percent of the variances in the two lifestyle factors accounted for. Consistent with this reasoning, alcohol intake was associated with age and sex, and only slightly with subjective well-being, but not with the other psychosocial factors.

In terms of smoking, two different analyses yielded a similar result. The regression analysis (including smokers only) showed a significant association between the factor “task properties” ($\beta = -0.21$) and the degree of smoking behavior, accounting for 5% of the variance in the number of cigarettes smoked per day. Using non-parametrical tests to compare smokers with non-smokers, again, non-smokers had higher scores on the factor “task properties”. This implies that desirable task properties such as task variety, qualification potential or decision authority – which are viewed by some investigators as salutogenic work characteristics – relate to relatively healthier smoking habits.

Cross-sectional analyses do not explain the direction of the observed association. However, it seems more likely that a low degree of beneficial task properties leads to a higher degree of smoking, than to assume that the number of cigarettes, a habitual smoker consumes, exerts an adverse influence on the individuals' perception of his or her working context.

As per self-reported alcohol intake, the regression analysis explained 20% of the variance. Being older ($\beta = 0.35$), being male ($\beta = 0.27$) and, to a lesser degree, lower subjective well-being ($\beta = -0.11$), were all associated with higher alcohol intake. However, median self-reported alcohol intake in both age groups are compatible with those conferring a decreased risk for CAD (Stampfer et al., 2000).

Physical activity was significantly related to "subjective well-being" ($\beta = 0.12$), indicating that the lower subjective well-being, the less physically active employees were. It is likely that among the 403 participants, for some, the causal direction was from higher physical activity to a better subjective well-being, while for others, the factors contributing to impaired well-being, such as "vital exhaustion", resulted in reduced physical exercise. Prospective studies are needed to further elucidate this observation.

It has been hypothesized that a major pathway leading from unfavorable psychosocial conditions to CAD is via adverse health behavior. If this holds true, our analysis of employees derived from the same industrial site should have yielded stronger associations between psychosocial variables and lifestyle factors than those we observed. Our data thus support the notion that in this particularly cultural context of Bavarian industrial employees, adverse psychosocial conditions may exert their impact on cardiovascular health to a considerable part independently from altering lifestyle behavior. This opens promising avenues for future research on the effect of work-related risk conditions via neuroendocrine pathways on known biological risk factors (e.g. a hypercoagulatory state in subjects with chronic stress) (von Kanel, Mills, Fainman, & Dimsdale, 2001).

The strength of this work comprises the particular study population, which resembles a previously well-described cohort in a landmark WHO-study on risk factors for CAD (Koenig et al., 1999). Our study sample was considerably homogenous in terms of important socio-economic health determinants such as access to health care and domestic family income (Kaplan & Keil, 1993).

A possible caveat of the present study could be its cross-sectional nature. Our primary intention was to investigate the association between health behaviour and work conditions, both independent risk factors for CAD. We cannot exclude that more long-term associations exist; for instance, persistent adverse work conditions might increase the long-term likelihood of habitual alcohol intake as an expression of a failure to cope with high levels of perceived job stress (Seeman & Seeman, 1992). A further limitation of the study is that lifestyle-indices were based on self-reported data. Social desirability bias may have led to underreporting of smoking and alcohol intake as well as to over-reporting of physical activity (Leary, Tchividjian, & Kraxberger, 1994). However, at present, the Bavarian cultural context shows a permissive attitude towards alcohol (beer) consumption. In contrast to America cigarette smoking is not banned from public premises or work places in Germany and the attitude is indifferent to favourable towards regular physical exercise (Wagenaar, Harwood, Toomey, Denk, & Zander, 2000) (Croghan et al., 2001) (Cavill, 1998). Further reduction in self-report bias may arise from having conducted the study at workplace, and that measurements referred specifically to conditions at work or resulting from work. As stated above, we acknowledge that our psychosocial factor panel, and the work place variables in particular, might mediate their coronary threat via a variety of other established coronary risk factors (Belkic et al., 2000), e.g., procoagulant changes (von Kanel et al., 2001), which have recently been related to unfavorable work conditions.

In conclusion, our data suggest that psychosocial variables and lifestyle behavior show modest associations at best. The findings suggest that pursuit of independent approaches in terms of changing both lifestyle behavior and psychosocial factors at work, may have their own right in primary prevention of cardiovascular morbidity and mortality. Given that we investigated healthy employees in a cross-sectional design, further studies need to show whether our findings hold true in employees with established CAD, and whether interventions, which target psychosocial factors at work, may improve cardiovascular outcome related to job stress.

10 General discussion

The present thesis addresses the validity of the concept of allostatic load in a working context. To investigate this objective, two studies have been conducted. One dealt with the association of psychosocial factors and allostatic load, the other one dealt with the association between psychosocial factors and health-related behaviours. Both associations are implied by the allostatic load model (see figure 1, p.10) (McEwen, 1998a). The following sections discuss the two studies with reference to the existing literature and with regard to the allostatic load model. The thesis closes with limitations of the study and implications for future research.

10.1 The association between psychosocial factors and indicators of allostatic load

In the first study, values from 537 employees at a German manufacturing plant were captured on the SF-12 General Health Questionnaire, the short version of the Maastricht Questionnaire, a symptom checklist, and the SALSA. Furthermore, biomedical data on 14 parameters associated with allostatic load were obtained from a subset of 332 of these subjects. In a first step, principal component analysis on *all* variables was carried out, which yielded three psychosocial factors (termed “task properties”, “social support at work”, and “perceived well-being”) and five biomedical factors (termed “ageing”, “inflammation”, “fat metabolism”, “body constitution”, and “urinary excretion”).

The psychosocial factors showed no association with an allostatic load summary score. Nevertheless, the psychosocial factors did explain 12.4% of the variance in a second-order “biological health status” factor, which is constituted by the shared variance of the five first-order biomedical factors. “Social support at work” had a positive influence on “perceived well-being”, which in turn had a positive influence on “biological health status”. The direct positive influence of "social support at work" on "biological health status" was not significant at $p < 0.05$, but marked a trend. Also trends are the positive influence of "task properties" on "perceived well-being" and the negative influence of "task properties" on "biological health status".

Although there are numerous studies showing an association between several psychosocial factors and health outcomes like cardiovascular disease (for a review see (Hemingway & Marmot, 1999)), a recent study found no association between psychosocial factors (i. e. social support, decision latitude, and job demands) and allostatic load (Schnorpfeil, 2001). This study used the original allostatic load summary score as described by Seeman (Seeman, Singer et al., 1997). The present study might be able to solve the contradicting results. There was also no association between psychosocial factors and the allostatic load summary score, but when using a more elaborate approach to model allostatic load, the association could be established, thus supporting the vast majority of evidence from prospective cohort studies on this issue (Hemingway & Marmot, 1999).

Going into detail, the strongest influence on biological health is exerted both directly and indirectly via perceived well-being by social support. This finding is also consistent with both theoretical considerations like those in Karasek and Theorell's job strain model (Karasek, 1990), and empirical evidence from prospective cohort studies (Berkman, 1983; Hedblad et al., 1992; Orth-Gomer et al., 1993; Ruberman et al., 1984). The findings regarding task properties are somewhat unexpected. High values on task properties like task variety, decision latitude, or qualification potential exert a positive influence on perceived well-being, which is in accordance with classical theoretical models on this issue (Hacker, 1978, 1980; Hackman, 1975; Udris et al., 1991; Udris et al., 1992). But they also exert a negative influence on biological health. Evidence on this issue is also controversial. While most studies found a positive influence of the above mentioned task properties and biological indicators of health (Bosma et al., 1997; Haan, 1988; Lacroix, 1984; Lynch et al., 1997), there is also evidence supporting the notion of a negative influence (Netterstrom et al., 1999). Part of this discrepancy might be due to different operationalisations of the various task properties or characteristics. However, the model established in the first study implies different directions for the direct and the indirect effect of the task properties. To the author's knowledge, no-one has so far separated direct and indirect influences on this issue. Thus, it is no surprise that the influence of task properties on biological health status is somewhat controversial, dependent on the relative strengths of the direct and indirect influences.

By speaking of an influence of "perceived well-being" on "biological health status", one implies a causal relationship. Anyhow do the arrows in a structural equation model suggest certain dependencies. As already outlined in the section on structural equation modelling, do causal relationships require an association, a certain temporal sequence, and the seclusion of confounding variables. The most problematic requirement is certainly that of the temporal sequence. From cross-sectional data, it cannot be stated, whe impaired perceived well-being leads to a deterioration in biological health status or vice versa. Nevertheless is there some evidence that the direction as implied by the model might be correct, although there are surely interdependencies at work. "Perceived well-being" is to a large degree (β = -0.90) defined by vital exhaustion. In a series of studies, Appels has shown that vital exhaustion has a prognostic validity for cardiovascular disease, particularly myocardial infarction (Appels, 1980; Appels & Mulder, 1988). Appels also ruled out confounding by underlining subclinical cardiovascular disease, thus gathering strong evidence for a preceding role of vital exhaustion (Appels & Mulder, 1989). Exactly this association of vital exhaustion and cardiovascular disease might be hidden in the presented model. On the one hand vital exhaustion strongly contributes to perceived well-being in a negative way, while perceived well-being in turn exerts an positive influence biological health status. Biological health status again is defined by blood pressure, cortisol excretion, C-reactive protein, LDL, cholesterol, HDL, body mass index, and waist to hip-ratio, taking only significant paths into account. This resembles very much a list of risk factors for cardiovascular disease (Kannel, 2000; Lenfant et al., 1998; WHO, 1994). The relevance of these results within the concept of allostatic load will be discussed further below.

10.2 The association between psychosocial factors and health-related behaviours

In the second study, a subset of 403 individuals from the first study, with complete data with regard to the research question, were under investigation. Again, values for the SF-12 General Health Questionnaire, a symptom checklist, the short form Maastricht Questionnaire, and the SALSA were used. In addition, self-report data were obtained for levels of cigarette smoking, alcohol consumption, and physical activity. Like in the first study, principal component analyses were carried out with the psychosocial variables to yield the factors “perceived well-being”, “task properties”, and “social support at work”. Further calculations focussed on associations between these three psychosocial factors and any of the three health-related behaviours or so-called lifestyle factors.

“Task properties” were found to be associated with the average number of cigarettes smoked per day, and “perceived well-being” was slightly associated with physical activity. “Social support at work” was not associated with any of the three lifestyle variables. All findings remained unchanged after controlling for age, sex, job status, mean blood pressure, LDL/HDL ratio, and levels HbA_{1c}.

The negative association between beneficial or salutogenic “task properties” and the number of cigarettes smoked has been shown in two analyses. There was a significant difference in the rating of “task properties” between smokers and non-smokers on the one hand, and on the other hand there was a dose-response relationship between “task properties” and cigarette smoking within the group of smokers. It is not possible to tell the direction of this relationship from cross-sectional data. However, it seems rather plausible that task properties like task variety, qualification potential, qualification demands and decision latitude exert an influence on smoking, than to hypothesize that the number of cigarettes smoked influences the perception of an employees working conditions as either beneficial or maleficent. Nonetheless, there is of course the possibility that the association is mediated by one or more underlying variables. The common notion that “stress” in general terms – best represented by “subjective well-being” within this study – leads to increased levels of smoking is discussed controversial in the literature (Kassel, 2000; McCann & Lester, 1996; Naquin & Gilbert, 1996; Posner, Leitner, & Lester, 1994) and could also not be affirmed by the present results.

The association between “subjective well-being” and physical activity again poses the question of the direction of the relationship. Here, it is not as easy as for “task properties” and smoking to argue theoretically for the plausibility of one or the other direction. Rather, it seems more realistic to hypothesize interdependencies between the two variables. On the one hand, a certain level of physical activity might exert a positive influence on perceived well-being, which might again be in part be mediated by the improvement in the objective biological health status (Brown, 1992; Fox, 1999). On the other hand, indicators of “subjective well-being” might also influence the level of physical activity. Especially vital exhaustion, the main indicator of “subjective well-being”, represents feelings of fatigue, demoralization and lack of energy, which most certainly reduces the level of physical activity (Appels & Mulder, 1988, 1989).

Rather unexpectedly, alcohol intake did not show a substantial association with any of the psychosocial factors. There was only a weak association between the level of alcohol consumption and “subjective well-being”. Nevertheless, this association is in accordance both with the general belief that impaired well-being might go along with increased alcohol consumption and with reports from the co-morbidity of depression and alcohol abuse on a clinical level (Cargill, Emmons, Kahler, & Brown, 2001; Gilman & Abraham, 2001; Wang & Patten, 2001). However, the median self-reported alcohol intake for all considered subgroups fell within a range that is not associated with increased health risk, it was rather still compatible with levels of alcohol consumption that have been shown to decrease the risk of coronary artery disease (Stampfer et al., 2000).

Although social support has been shown to bear strong associations with health outcomes, especially related to cardiovascular disease (Cohen & Syme, 1985; Greenwood et al., 1996; Shumaker, 1994; Wallston, 1983), the present study did not reveal any association with health-related behaviors that also belong to the major risk factors for cardiovascular events.

In conclusion, the results of this study showed that the associations between the psychosocial factors “task properties”, “subjective well-being”, and “social support at work” and the health-related behaviors smoking, alcohol intake, and physical activity were modest at best. These results question the hypothesis that a major pathway from psychosocial factors to adverse health outcomes is via health-related behavior. This notion will be discussed in detail in the following section on the relevance of the presented studies for the allostatic load model. Furthermore, limitations of the present studies that have to be borne in mind are considered in section 10.4.

10.3 Relevance of the results for the Allostatic Load model

The previous sections have discussed the results of the studies considering the literature in the field individually. The present section views the results in the context of the allostatic load concept. Figure 9 recapitulates the model of allostatic load and where the investigated research objectives are placed within the model.

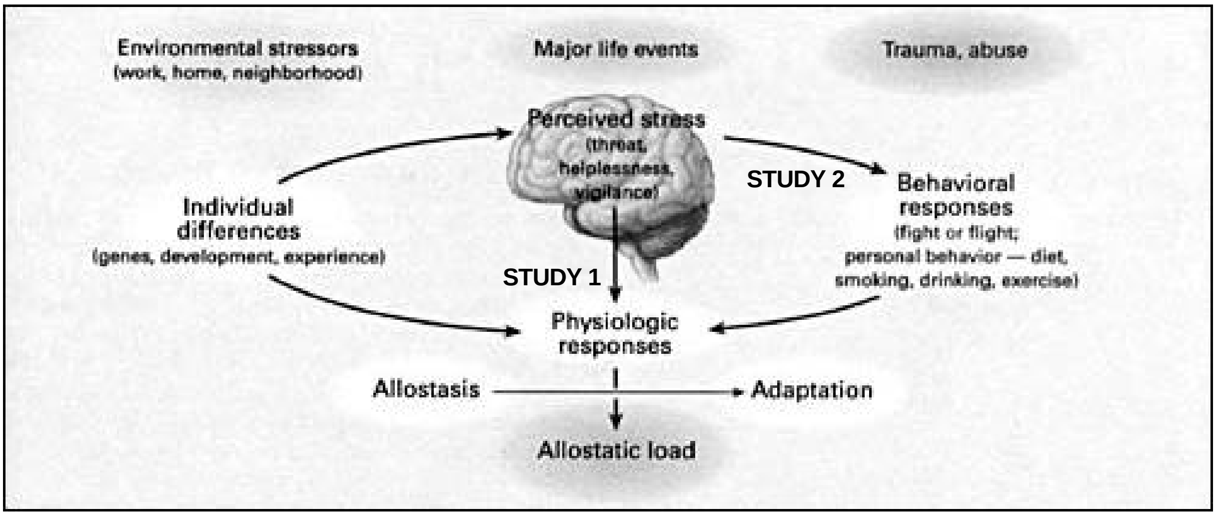

Figure 9. The placement of the two studies within the framework of allostatic load (McEwen, 1998a, p.172).

The first study set out to look for the hypothesized association between “perceived stress”, which is a result of “environmental stressors” like work stress amongst others, and “physiologic responses” that contribute to “allostatic load”. An enormous variety of studies has been done on the association between stressful events or situations and health outcomes (for example see the review of (Hemingway & Marmot, 1999)), as well as on the association between physiologic responses (primary mediators and secondary outcomes alike) and health outcomes. Also, numerous studies have been carried out that showed associations between stress and certain physiologic responses (Antonovsky, 1979; Chrousos et al., 1995; Cohen et al., 1991; Ehlert & Straub, 1998; Ely, 1995; Fisher & Reason, 1988; Laudenslager, 1987; McEwen & Stellar, 1993; Semmer, 1997). Nevertheless, the evidence on the concept of allostatic load is sparse. The MacArthur studies of successful aging affirmed an association between allostatic load on the one hand and cognitive and physical deficits and increased mortality on the other hand (Seeman, Singer et al., 1997). To the author's knowledge, there has only been one study to date that investigated the association between measures of perceived stress and adverse work conditions and physiologic responses in the form of an expanded allostatic load summary score (Schnorpfeil, 2001). This study failed to show the mentioned association.

The first study of the present thesis set out to overcome possible methodological problems inherent in the allostatic load summary score used by Schnorpfeil and in the original work by Seeman and others (Seeman, Singer et al., 1997). This notion has also been suggested by Seeman herself and since been considered by Karlamangla (Karlamangla, unpublished). While Karlamangla used weighing systems in form of canonical correlation analyses for the components of allostatic load, study 1 of this thesis employed the structural equation modeling approach. The results of study 1 support the hypothesized pathway between perceived stress and physiologic responses contributing to allostatic load highlighted in figure 9.

Study 2 of the present thesis investigated the assocation between "perceived stress" and "behavioral responses", also hypothesized within the model of allostatic load (see figure 9). Like in study 1, perceived stress again was operationalized by perceived or subjective well-being on the one hand and by influences exerted from the environment in the form adverse work conditions. The investigated behavioral responses were restricted to smoking, alcohol consumption, and physical exercise. The associations, reported in earlier sections, were modest at best, which suggests that perceived stress and adverse psychosocial factors exert their influences on health outcomes mainly through pathways other than through health-related behavior. With that regard, the hypothesized pathway of the allostatic load model between perceived stress and health-related behavioral responses could not be established.

Possible alternative pathways through which perceived stress exerts its established influence on health outcomes – especially cardiovascular disease - include neuroendocrine impacts on known risk factors like hypercoagulatory states (Cavusoglu et al., 2001; Siegrist, Peter et al., 1997; Tsutsumi, Theorell, Hallqvist, Reuterwall, & de Faire, 1999; von Kanel et al., 2001).

In conclusion, one of the studies of this thesis could confirm a pathway hypothesized by the allostatic load model, while the other study could not confirm another hypothesized pathway. Regarding both studies as well as all reviewed evidence belonging to the scope of the framework of allostatic load, the model depicted in figure 9 is very well able to explain a wide variety of results around the question, how working environments, living environments, and socio-economic conditions affect health or disease. According to McEwen and colleagues, this is the major goal of the allostatic load concept (McEwen & Seeman, 1999). Therefore, the model has to be granted a legitimate function within the area traditionally termed as "stress" research. However, its generality makes the model quite vague in its predictive qualities. The main value of the model for clinical implications is supposed to be the assessment of allostatic load as a predictor for adverse health outcomes. Thus, it might be useful as a framework to diagnose the burden, the body has already accumulated due to stressful events. As study 1 has shown, exactly the "what" and "how" of this measurement seems to be crucial for the validity of the whole concept. This issue will also be discussed in the following section on the limitations of the studies within this thesis.

10.4 Limitations of the present studies

There are a few aspects that have to be regarded when interpreting the results of the present studies. First, it would have been desirable to integrate the research objectives of both studies into one structural equation model representing the structure of the allostatic load model. Due to a relatively small sample, this was not possible. Structural equation modeling is an approach that needs enormous sample sizes to evaluate complex models. The model, which was employed in study 1 was probably the most complex model that could just be calculated. For a model incorporating both research objectives, a sample size of at least 2000 would have been necessary. If one wants to employ the more robust “asymptotically distribution free” estimation method, sample sizes around 5000 are regarded as adequate. Such an integrated model would allow to test several associations implied by the allostatic load model simultaneously, which would be very revealing.

Apart from the restricted sample size and related statistical limitations, our study population comprised less than an eighth women. This fact renders it nearly impossible to study the influence of sex adequately. Future studies will have to consider this influence in relation to the allostatic load concept.

Another limitation arises from the cross-sectional nature of our data. As noted earlier, the allostatic load model implies several directional associations that are also represented by one-headed arrows in the structural equation model or implied in the associations investigated in study 2. Nevertheless, directionality cannot be proven from cross-sectional data, because one never knows for sure the temporal sequence of the investigated variables. For some associations, logical arguments speak strongly in favour of the direction implied by the allostatic load concept. For others, we will carry out calculations with the longitudinal data that will by assessed in a three-year follow-up to prove the underlying directionality.

A final limitation concerns the generalisability of the presented results. On the one hand, our results are restricted to the working context and to middle-aged employees, who were mainly men. On the other hand, the results from study 1 are at large restricted to cardiovascular disease. This aspect has two reasons. First, the original allostatic load summary score itself employs mainly mediators and risk factors for cardiovascular disease. Second, the additional factors included in the allostatic load concept were not significant within the model in study 1. This again stems from the choice of psychosocial factors, which were explicitly chosen for their association with cardiovascular disease. Thus, a more holistic investigation of the allostatic load concept including other health outcomes than cardiovascular events would be desirable, although this poses the problem to find associations with a multi-factorial outcome measure.

10.5 Implications for future research

A few options for future research have already been outlined in the previous section, because they arise directly from the limitations of the present studies. The most important one being the inclusion of a more representative number of women. Although the quota of women in the working context steadily increases, there have only been rather few studies on the effects of job characteristics on adverse health outcomes who focussed on women (Brisson et al., 1999; Cheng, Kawachi, Coakley, Schwartz, & Colditz, 2000; Williams et al., 1997). Especially the validity of the allostatic load model for women will have to be tested to confirm the results from the present thesis.

Further possible steps to increase the generalisability of the presented results include the extension of the investigated stressors beyond the scope of the working context. Particularly the concept of social support at home and in a non-working environment promises substantial influence on health and well-being (Semmer, 1997; Shumaker, 1994) and needs to be regarded in future studies. To validate the allostatic load model on an even broader basis, it is also inevitable to consider measures for the model components “major life events”, “trauma, abuse” and “individual differences” (McEwen, 1998a)(see figure 9, p.101), whose general influence on health has already been shown (Baumann & Perrez, 1998; Felitti et al., 1998; Judge, Bono, & Locke, 2000; Newbury-Birch & Kamali, 2001; Repetti, 1999; Wadhwa et al., 1993; Yehuda et al., 2000).

There are also some methodological considerations that might play a role for the planning of future studies in this field. First, measurement of physiological parameters only took place at one instance. This is a rather unstable basis due to large measurement errors on the one hand and it does not account for diurnal cycles or aspects of variability or responsibility of these quickly changing physiological systems on the other hand (Kamarck et al., 1998; Kirschbaum & Hellhammer, 1999; Pickering et al., 1996). The assessment of physiological parameters over longer periods of time is therefore desirable to better match subjective feelings of well-being or being stressed to objective parameters (Fischer, Calame, Dettling, Zeier, & Fanconi, 2000; Myrtek, Fichtler, Strittmatter, & Brugner, 1999). Talking about gaining more objective data, another interesting question for future investigations is, whether self-reported measures of work characteristics and social support go along with more objective external evaluations of these aspects and what implications might arise from possible discrepancies.

A last suggestion for studies to-come regards the employed statistical methods. Structural equation modeling proved to be a promising approach for testing complex models like that of allostatic load. The comparison of the fit of different models to specific data will permit statements about the adequacy of several models in relation to each other. The application of this method is therefore strongly recommended, although it claims very large sample sizes.

Apart from all theoretical considerations, one will always have to constrain the number of variables to assess to meet practical requirements. In that sense, the present thesis was restricted to those aspects that are regarded as downright central for the investigated research objectives.

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Curriculum Vitae

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